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THE INTRAPERITONEAL TRANSPLANTATION OF ENDOMETRIAL TISSUE

AN EXPERIMENTAL STUDY *

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In recent studies already published,[1] it has been shown that rabbit endometrial tissue when sown in minute fragments in the peritoneal cavity of the same animal behaves much like the cells cast loose from an ovarian cystadenoma or carcinoma, becoming implanted on the peritoneum, subsequently to grow and invade underlying structures. These experiments were undertaken in an endeavor to seek further light on the plausibility of the theory of Sampson in explanation of the presence of endometrial tissue growing on and penetrating many pelvic and lower abdominal viscera. In the human being this ectopic endometriosis is found only in women, usually between the ages of 30 and the menopause, i. e., during the latter period of the menstrual epoch, and is often associated with similar tissue in the ovary frequently in the form of a menstruating endometrial cyst. The distribution of the endometrial tissue in patients with this condition is similar to that of the implants disseminated from certain ovarian carcinomas.[2] The clinical and pathologic picture of Sampson's syndrome presents a combination of facts which in itself, without regard for the success of experimental procedure, places his theory in a strong position.

Endometrium has been transplanted successfully by Leo Loeb [3] and his coworkers in the guinea-pig's ear and abdominal wall, and by

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1. Jacobson, V. C.: The Autotransplantation of Endometrial Tissue in the Rabbit, Arch. Surg. **5**:281, 1922; Further Studies in Autotransplantation of Endometrial Tissue in the Rabbit, Am. J. Obst. & Gynec. **6**:257, 1923.

2. Sampson, J. A.: Endometrial Carcinoma of the Ovary, Arising in Endometrial Tissue in the Organ, Arch. Surg. **10**:1, 1925.

3. Hesselberg, C.; Kerwin, W., and Loeb, L.: Auto- and Homoiotransplantation of the Uterus in the Guinea Pig, J. M. Res. **38**:11, 1918.

Stilling [4] in the rabbit's spleen, but in 1922 I was the first to sow such tissue in the peritoneal cavity and to produce peritoneal implantation thereby. In 1924, Katz and Szenes [5] in Peham's clinic in Vienna, and recently Blair Bell [6] of Liverpool, have confirmed these findings in the rabbit. In all of these studies of course autoplastic grafts were used.

There are certain optimum conditions for successful implantation on the peritoneum, both in man and in the experimental animal. First, the endometrium whether with or without stroma must be viable when it reaches the peritoneum; second, the peritoneum must be injured in some way at that point so that the fibrin precipitated may hold the epithelium in place in a nutrient field. The primary injury in man is probably caused by the irritating effect of the escaped menstrual blood. In the experimental animal the peritoneum is damaged by exposure to the air during the operation, by handling of the viscera and by general operative trauma, and to some extent by free blood. The influence of the several factors is being studied by Sampson in his human material, and will be the subject of a paper soon to be published by him.

Endometrium is a unique tissue, being subject to many hormonal influences and capable of extraordinary regeneration and hyperplasia. Most, though not all, of the misplaced endometrial tissue encountered in man and experimentally presents the same general picture as the lining of the fundus uteri. The changes of menstruation, pregnancy and the menopause, whether natural or artificially produced, are as a rule, faithfully reproduced in the most remotely situated ectopic growth. The reader is referred to Sampson's works for a more comprehensive account of this general subject.

The writer's experiments on rabbits may be summarized as follows: In a series of nineteen animals the intraperitoneal transplantation of endometrium during oestrus was successful in sixteen, or 84 per cent. In six animals so treated during the resting stage there was one positive result. In six animals operated on during pregnancy there were implantations in two, or 33 per cent. On the basis of these results an increased vitality or "virulence" may be assumed for endometrial tissue during oestrus. Five rabbits were subjected to complete oophorectomy, and at the same time intra-abdominal transplantation of endometrial tissue was done. In all of these animals growths were obtained, but they were much smaller than in the uncastrated, partaking of the same atrophic

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4. Stilling, H.: Versuche über Transplantation. IV. Mitteilung. Das Ergebnis der Transplantation von Uterusgewebe in de Milz, Beitr. z. path. Anat. u. z. allgem. Path. **47**:499, 1910.

5. Katz and Szenes: Untersuchungen über die Verpflanzung des Endometriums in die Peritonealhöhle beim Kaninchen, Zentralbl. f. Gynec. **44**:2400, 1924.

6. Bell, Blair: Personal communication.

changes affecting the uterus following deprivation of the ovarian principle. The implants were invariably cystic adenomatoid structures, often multilocular, and were found on the broad ligament, vagina, uterus, urinary bladder and large intestine. No evidence was obtained in favor of the view that endometrial tissue can be formed by metaplasia of mesothelium (figs. 1, 2, 3, 4 and 5).

It has been appreciated all along that the entire human picture of ectopic endometriosis could not be duplicated in nonmenstruating animals. The rabbit sufficed for the demonstration of the fact of peritoneal implantation, but no hemorrhage into an implant could be expected. Corner has shown that the primate *Macacus rhesus* when kept in captivity under proper hygienic conditions can menstruate every four weeks or thereabouts. Not all in a given group are likely to do so, however, and amenorrhea for many months at a time is not uncommon when a male is not provided. Coeliotomy such as is necessary in getting endometrium under aseptic conditions would probably decrease the regularity of oestrus in any primate available.

Five *Macasus rhesus* monkeys, about 18 months of age and in good condition, were subjected to coeliotomy under ether anesthesia, a hysterotomy done through an incision on the anterior uterine wall and a thorough curettage. The curettings were further divided into minute pieces, then sown in the abdomen, and some placed beneath the peritoneum in a few specific locations so that there would be less difficulty in identifying the "takes" later.

EXPERIMENTAL WORK

Monkey 5.—The animal was menstruating, the endometrium being swollen, reddened and friable, the tubes congested. On Oct. 15, 1924, a transplantation was made into cul-de-sac, free into the peritoneal cavity, and a few pieces were inserted into a cleft in the right ovary. Three weeks later the animal died from some unknown cause. The gross changes, with the exception of some adhesions about the uterus, were not remarkable. Microscopic examination showed several glands of endometrial type growing just within the external layers of the uterine muscle on its posterior surface and a few glands of similar nature attached to the serosal surface and partly surrounded by scar tissue, in which there were a few hemosiderin granules (figs. 6 and 7). No endometrial tissue was present in the ovaries.

Monkey 1.—On Oct. 15, 1924, transplantation was made beneath the peritoneum of the posterior surface of the uterus and at the junction of the left tube and uterus. The endometrium was in the resting stage. The animal was killed, June 12, 1925. There were numerous parasitic lesions on the intestines, mesentery and omentum, probably due to *Pneumonyssus foxi*. No transplanted endometrial tissue was found anywhere.

Monkey 2.—This animal was operated on Oct. 15, 1924. The same procedure was followed as in monkey 1. Monkey 2, was killed, June 12, 1925. The uterus and the tubes were congested and bound together by adhesions. There were several minute nodules, a millimeter or less in size, on the posterior wall of the

uterus near the tip. There was a prominent hysterotomy scar. Microscopic examination showed several single glands of endometrial type just beneath the serosa and in adjacent tags of fat. There was also a nodule about 3 mm. in size in the muscle wall approaching close to the endometrium and also nearly reaching the serosa. This nodule consisted largely of muscle, but on the endometrial side contained many endometrial glands with stroma. Serial sections showed no connection between this growth and the lining of the uterus. It probably arose from a piece of endometrium, possibly with some uterine muscle, transplanted beneath the peritoneum of the uterus. The single glands found elsewhere on the looser tissues about the uterus doubtless represented true implants. The stroma and glands were like those of the regenerated endometrium, there being some vascular dilatation but no stromal hemorrhage (figs. 8 and 9).

MONKEY 3.—This animal was operated on, Oct. 15, 1924. The same procedure was followed as in monkey 2 except that some endometrial scrapings were inserted beneath the serosa of the left ovary. The endometrium was in the resting stage at the time of the operation. The animal was killed, Oct. 16, 1925. The uterus (fig. 10) and tubes were slightly congested. There were indurated adhesions between the bladder and uterus. The cul-de-sac was obliterated by an abscess which was well encapsulated. The omentum was adherent to the fundus uteri. The right ovary was cystic, the left ovary normal. Microscopic examination revealed many endometrial glands in the vesico-uterine adhesions, but with no characteristic stroma. Several glands were present in the hysterotomy scar (figs. 11 and 12). There were some larger gland masses with a small amount of endometrial stroma in the loose connective tissue in this same region. The right ovary contained several follicle cysts, the left was normal. There was no endometrial tissue in the ovaries. There was peritoneal exudate on the various pelvic viscera. There were also peritoneal inclusions but none in any way resembling endometrial glands.

MONKEY 4.—Operation was performed on Oct. 15, 1924; the same procedure was followed as in monkey 3 except that a scraping of endometrium had been inserted beneath the serosa on the right posterolateral surface of the uterus; endometrium resting. The animal was killed, Oct. 16, 1925. The uterus and tubes were swollen and reddened. The omentum was adherent to the fundus uteri, and a nodular induration was felt at the point of attachment. On the left posterolateral surface of the fundus there was a bluish-red nodule about 2 mm. in diameter, with a slightly raised contour and fibrous tissue reaction about it. On the right posterolateral surface surrounded almost entirely by dense scar tissue was a bluish-red bleb which looked much like that on the left side. There were adhesions between this mass and the tube and ovary on that side.

The endometrium was in active menstruation, thickened and hemorrhagic. Microscopic examination revealed a menstruating uterus, with large masses of endometrium being cast off from the middle third but more intact in the lower and upper thirds (fig. 14). Beneath the serosa on the left posterior surface was a menstruating endometrial growth with a characteristic stroma, which was invading the uterine muscle (fig. 16). Some of the glands were dilated, forming small cysts containing blood and epithelium. Many scattered endometrial glands were present on other parts of the uterus but with little or no stroma. There was marked vascular dilatation about them, however. In the left ovary there was a growth of glands not exactly like the endometrium,

having a slightly higher epithelium with clearer cytoplasm. The stroma about this tissue was hemorrhagic, and indicated that in all probability it arose from a curetting inserted beneath the serosa at the operation (fig. 16). A corpus luteum and many ripening follicles were also present.

COMMENT

In four of five monkeys of about the same age the intraperitoneal transplantation of endometrium was successful. The sowing free in the abdominal cavity of scrapings of normal endometrium resulted in implantation on the surface of the uterus and adhesions about it. Implants were found only on pelvic viscera. While there may be an element of gravity involved, this was probably due largely to the fact that the uterus and adnexa were subjected to the greatest trauma at operation, thus injuring slightly but sufficiently the peritoneum which by means of a fibrinous exudate was able to anchor the foreign tissue long enough for nutrient channels to be established. It is also possible that microscopic implants were overlooked on the intestines, but if present, they were doubtless very few.

The reaction to the implantation could be studied in material three weeks, eight months and twelve months, respectively, after the primary dispersion at operation. At three weeks, fibroblasts and a few mononuclear phagocytes containing hemosiderin had accumulated about an implant found on the serosa of the uterus. At eight months a greater degree of fibroplasia with little if any leukocytic reaction was present, and some glands had begun to invade the uterus. The glands were similar to those in the fundus uteri, and when stroma was present with the implant it showed engorgement when the endometrium did. At twelve months the degree of reaction to the implant did not differ appreciably from that of eight months. In only one monkey was menstruation at its height when it was killed twelve months after operation. Menstruating endometrium was found in the ovary where it had been inserted and beneath the serosa of the uterus where it had become implanted.

No definite information one way or the other was gained as regards the power of endometrium to change fibroblasts into typical endometrial stroma cells. It is probable that all or nearly all of the endometrial scrapings contained stroma cells when cast loose after hysterotomy, so that no conclusions can be drawn other than that the stroma probably developed from preexisting endometrial stroma.

The endometrial tissue placed in the ovary in three monkeys stayed "put" or lived in only one, and in this particular animal there was hemorrhage into the stroma about the transplant, similar to that in the menstruating uterus. That a hemorrhagic or "chocolate" cyst might

have been formed in time would seem a possibility although the menstrual life of the monkey may not be of sufficient duration for this to occur.

The extraordinary ability of the endometrium to replace itself after extreme injury such as follows menstruation is well shown in the monkey that died three weeks after all endometrium possible had been scraped from it. Regeneration of an intact and normal membrane was complete as it was in all the other animals.

SUMMARY

Intraperitoneal transplantation of endometrium has been studied in the rabbit and monkey (*Macacus rhesus*). In a series of nineteen rabbits, when the operation was performed during oestrus it was successful in sixteen, or 84 per cent. In six rabbits so treated during the resting stage only one showed a "stake." In six animals operated on during pregnancy there were implantations in two, or 33 per cent. An increased vitality or "virulence" is suggested for rabbit endometrium during oestrus. Ectopic endometrial growths in five castrated rabbits showed the same atrophic changes seen in the uterine cornua. The implants were invariably cystic adenomatoid structures, often multilocular, and were found on the broad ligament, vagina, uterus, urinary bladder and large intestine.

Five *Macacus rhesus* monkeys were subjected to hysterotomy, curettage and intraperitoneal transplantation of the curettings. In four animals ectopic growths were produced which were confined to the uterus and adhesions about it. Operative trauma was probably responsible for the localization of the implants in this region. In one monkey actively menstruating when killed ectopic endometrial tissue on the uterus and in the ovary was also menstruating.

The successful inoculation of the peritoneum of the rabbit and the monkey with their own endometrium, the general location of the growths produced, their histologic character, the manner of their development and their reaction to the ovarian hormone, are all in favor of Sampson's theory of the origin of most cases of ectopic endometriosis in the human being.

Fig. 1.—Posterior aspect of the uterus and its appendages of a rabbit that 150 days previously had been subjected to transplantation of its cornual mucosa. The animal was in heat when killed. At *a* and *b* are characteristic multicystic growths attached to and invading the fat of the broad ligament.

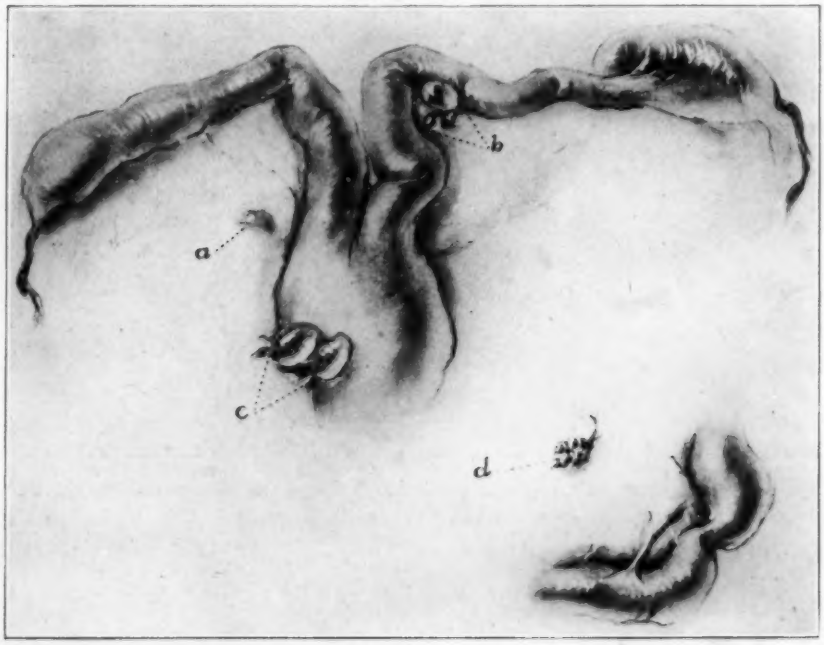

Fig. 2.—A rabbit treated similarly to that in fig. 1. At *a* is a submerged cyst of endometrial type; at *b* and *c* are cysts resulting from endometrial implants. At *d* is a group of small cysts on the anterior surface of the meso-salpinx.

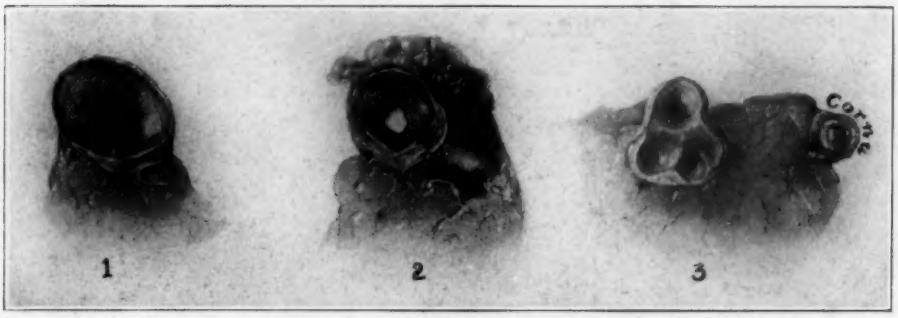

Fig. 3.—A typical endometrial implant about 150 days old, in the broad ligament fat of a rabbit; different levels.

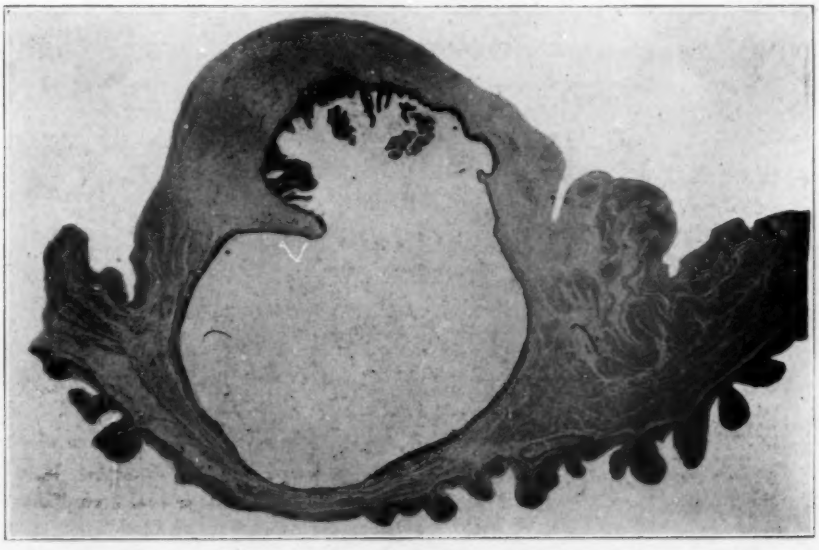

Fig. 4.—Endometrial implant on the anterior wall of the urinary bladder of a rabbit, 281 days after operation.

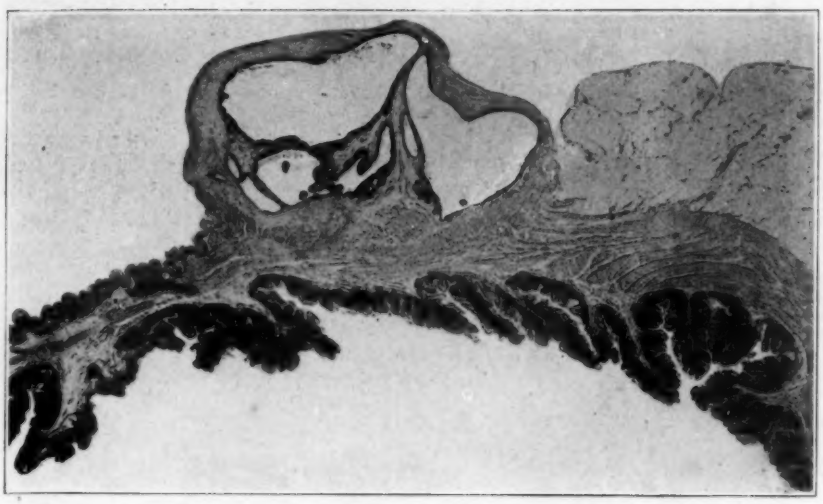

Fig. 5.—Endometrial implant 180 days old on a rabbit's large intestine.

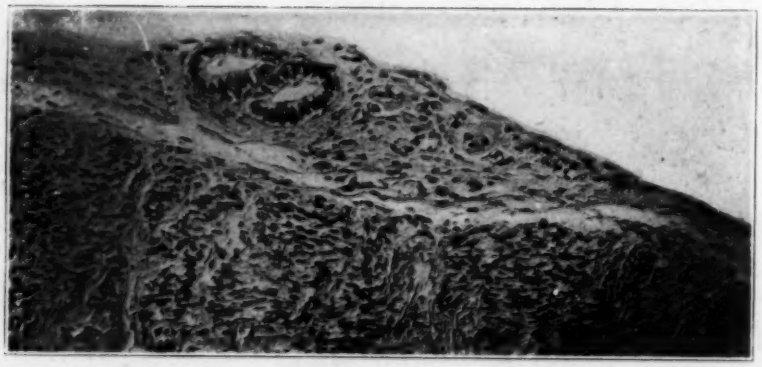

Fig. 6.—An implant three weeks old on the uterus of monkey 5. This is the earliest implant seen, and phagocytes containing hemosiderin are still present in the fibrous tissue about the glands. The animal was in heat at the time of operation.

Fig. 7 (monkey 5).—Endometrial glands growing near the surface of the uterus. These were derived from tissue inserted beneath the peritoneum and did not arise by implantation.

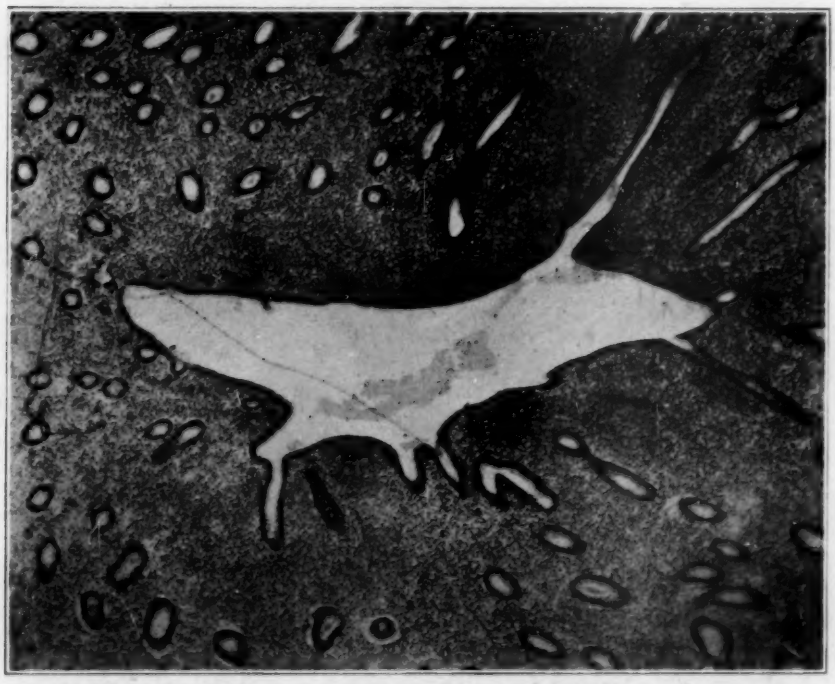

Fig. 8 (monkey 2).—Resting intact endometrium in uterus.

Fig. 9 (monkey 2).—A nodule in the posterior wall of the uterus, derived from endometrium buried there. The glands in this growth are identical with those in the lining of the uterus in fig. 8.

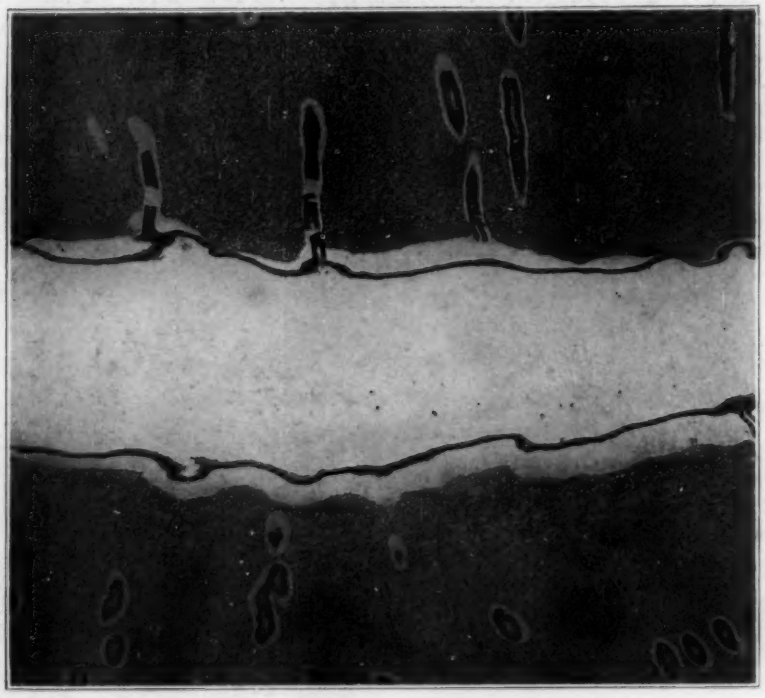

Fig. 10 (monkey 3).—Endometrium of uterus showing engorgement of the stroma.

Plate 6

Fig. 11 (monkey 3).—Implants in the adhesions between uterus and bladder. The scar along the line of the incision in the uterus is shown in the lower left quadrant, with several endometrial glands scattered about.

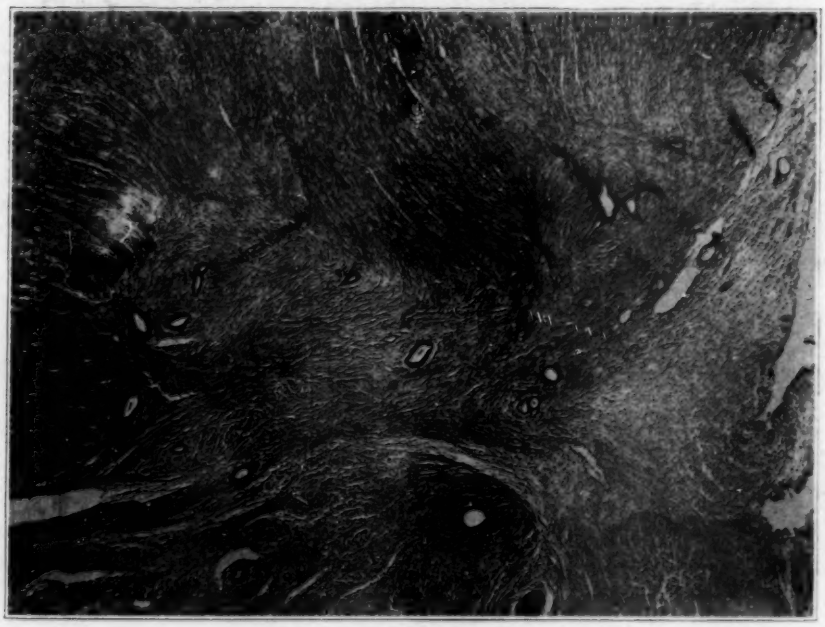

Fig. 12 (monkey 3).—Numerous endometrial glands without stroma in the hysterotomy scar.

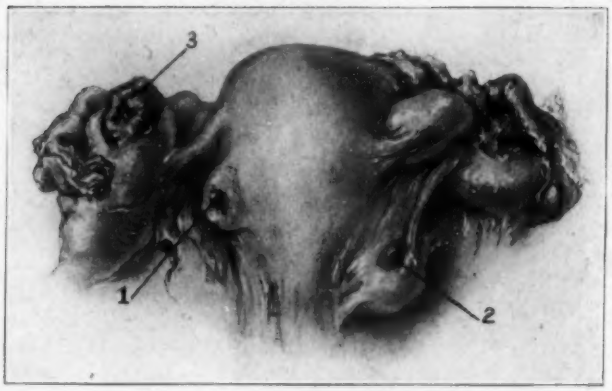

Fig. 13 (monkey 4).—A posterior view of the uterus and adnexa (×1.5). The right tube and ovary are matted together by adhesions. At 1 is the menstruating implant shown in fig. 16; at 2 is a mass of fibrous tissue containing dilated veins and menstruating endometrial tissue which had been inserted beneath the peritoneum at operation; at 3 is a ruptured corpus luteum in the left ovary.

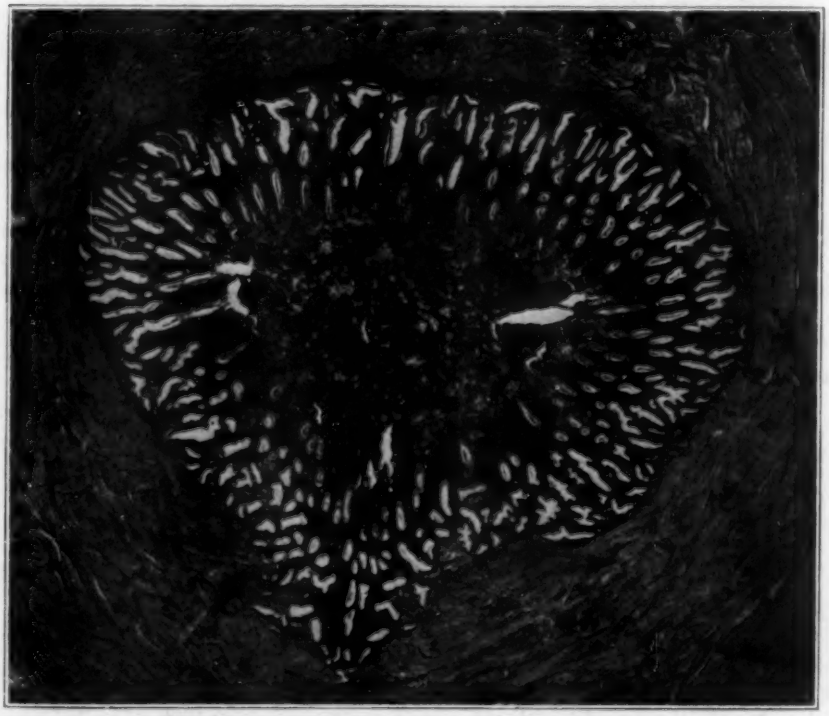

Fig. 14 (monkey 4).—A section through the middle third of the uterus showing menstruating endometrium with casting off of much lining tissue and hemorrhage into the lumen.

PLATE 8

Fig. 15 (monkey 4).—Menstruating endometrial tissue in the left ovary. The arrow points to the stromal hemorrhage. A rather thick celloidin section. The epithelium differs slightly from the endometrium elsewhere, being higher and with clearer cytoplasm.

PLATE 9

Fig. 16 (monkey 4).—A section of the uterus showing the menstruating mucosa and the menstruating implant on the left posterior surface. There might be some doubt as to whether this is a real implant or whether it had been buried there. No endometrium had intentionally been inserted on this side, so no doubt this is a true implant. In the human condition an overgrowth of fibrous tissue such as is shown here is not uncommon where invasion of underlying tissue occurs (× 8).

RELATION OF SUPRARENAL CORTEX TO THYROID AND THYMUS GLANDS*

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Articles on the thymus occupy a large space in the literature of clinical medicine and a small space in the literature of physiology. Indeed, there is no organ of such volume concerning which less is known. Our lack of knowledge of this organ applies almost equally to its anatomy (both embryology and histology), physiology and pathology. The methods that have yielded such valuable leads regarding the function of certain other organs of internal secretion, namely, extirpation and the use of extracts, have proved disappointing in the case of the thymus. However, there are certain special characteristics and outstanding clinical associations that have kept up a lively interest in the thymus in spite of the discouraging results of physiologic and chemical investigations. The fact that the thymus undergoes both physiologic and pathologic involutions; that in mammals the physiologic involution normally begins at sexual maturity and yet under certain conditions, as in exophthalmic goiter, acromegaly, Addison's disease and status lymphaticus, may remain uninvoluted or actually regenerate, suggest that the gland plays some important rôle, though obviously not vital, in the maintenance of the balance of action of other internal secretions, at least during the period of development in mammals.

There is a tendency today to exclude the thymus from the list of glands of internal secretion on the grounds that no proof of such a secretion exists, and that in its general morphologic reactions it resembles the other lymphoid tissues of the body. While both these statements are true at the present time, they indicate our lack of knowledge of this organ rather than a basis for excluding a possible internal secretion. I said proof of an internal secretion, for there is evidence of such a secretion in birds. In birds the thymus remains active throughout the period of active sexual life. Soli [1] pointed out in 1910 that fowls from which most of the thymus had been removed laid eggs with deficiently calcified shell membranes. He concluded that the thymus of birds was concerned in some way with normal calcium metabolism. Riddle,[2] in 1924, working with doves and pigeons, observed a group which on the diet used also produced soft-shelled eggs and, in addition, a deficiency of

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1. Soli, U.: Contribution à la conaissance de la fonction du thymus chez le poulet et chez quelques mammifères, Arch. ital. biol. **52**:353, 1909-1910.

2. Riddle, O.: Studies on the Physiology of Reproduction in Birds. XIX. A Hitherto Unknown Function of the Thymus, Am. J. Physiol. **68**:557, 1924.

albumin. He further found that the administration of from 5 to 20 mg. dried ox thymus daily corrected this defect.

My purpose is to present some recent experimental evidence so clear cut and so readily obtained that it must indicate some specific chemical interrelationships, particularly with the thyroid, gonads and suprarenals.[3]

EXPERIMENTAL RESULTS

1. Thyroidectomy hastens the physiologic involution of the thymus. This fact has been established by work carried out from several different directions. Many observers have noted atrophy of the thymus after thyroidectomy in rabbits, guinea-pigs, rats and dogs. The results of our series of sixty-six thyroidectomized rabbits of known age merely confirm these earlier observations. The parathyroids are not involved in producing this effect. Hoskins,[4] Utterstrom and others have noted that the thymus was larger in the young of rats and guinea-pigs fed with thyroid gland than in controls. Gudernatsch,[5] Uhlenhuth[6] and Romeis[7] have pointed out that feeding thymus delays the metamorphosis of frog and salamander larvae. Lastly, many pathologists have noted atrophy of the thymus in cases of infantile myxedema associated with atrophy or abscence of the thyroid. The conclusion, therefore, that the thyroid gland is necessary for normal thymus growth and function seems definitely established. In this connection it might be pointed out that neither a thymus nor a true thyroid has been found in animals below the *Petromyzon* (*lamprey*), though in this and all higher animals both are present. If this biologic association of the thyroid and thymus is proved to be constant, it would add further support to the view that the thymus and thyroid were somewhat antagonistic in their actions—a view that some observers have utilized in attempting to explain the thymus enlargement in exophthalmic goiter.

2. Gonadectomy delays thymic involution in both sexes. This fact has also been established and confirmed by a large group of observers

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3. Marine, D.: Manley, O. T., and Baumann, E. J.: The Influence of Thyroidectomy, Gonadectomy, Suprarenalectomy and Splenectomy on the Thymus Gland of Rabbits, J. Exper. Med. **40**:429, 1924.

4. Hoskins, E. R.: The Growth of the Body and Organs of the Albino Rat as Affected by Feeding Various Ductless Glands (Thyroid, Thymus, Hypophysis, and Pineal), J. Exper. Zool. **21**:295, 1916.

5. Gudernatsch, J. F.: Feeding Experiments on Tadpoles. II. A Further Contribution to the Knowledge of Organs with Internal Secretion, Am. J. Anat. **15**:431, 1913-1914.

6. Ühlenhuth, E.: Nature of the Retarding Influence of the Thymus upon Amphibian Metamorphosis, J. Gen. Physiol. **1**:305, 1918-1919.

7. Romeis, B.: Experimentelle Studien zur Konstitutionslehre. I. Die Beeinflussung minder veranlagter, schwächlicher Tiere durch Thymusfutterung. München. med. Wchnschr. **68**:420, 1921.

for all domestic animals and for man as well.[8] Gonadectomy alone will not prevent ultimate involution of the organ; nor so far as there is any evidence at present, does gonadectomy alone cause thymic regeneration. Some observers have claimed that gonadectomy alone can bring about regeneration of the mammalian thymus, but this is highly improbable. The data on which such conclusions were made are more rationally explained by assuming suprarenal involvement.

3. Suprarenalectomy not only prevents thymic involution, but actually causes regeneration even of the highly involuted organ of old rabbits. In young rabbits and rats before sexual maturity, suprarenalectomy causes further enlargement of the gland. This has been checked on both rabbits and rats, using litter mates as controls. In old animals (rabbits over 2 years and rats over 1 year of age) with highly involuted glands complete regeneration may take place if the animal survives suprarenalectomy long enough. In my experience with rabbits and Jaffe's [9] experience with rats, this takes from ten to fifteen days for its gross demonstration, and the few references in the literature stating that it has been observed in animals surviving double suprarenalectomy from one to five days are in our opinion inaccurate. The only earlier observations on this point were reported by Crowe and Wislocki,[10] who observed in four dogs that survived for some weeks the piecemeal reduction of the suprarenal gland, distinct enlargement of the lymphoid tissue throughout the body and also apparent thymus enlargement. In addition to the statistical data on thymic regeneration in rabbits and rats following double suprarenalectomy, Jaffe [11] has directly controlled a series of experiments by removing a fragment of the thymus for histologic examination before removing the suprarenals. Regeneration of the thymus after suprarenalectomy occurs in animals even though they are losing weight and in the presence of chronic infections—factors known to cause pathologic or accidental involution.

Summing up, then, it has been shown on large series of rabbits and rats, both statistically and by directly controlled experiments, that suprarenalectomy exerts a powerful stimulating influence on the thymus. In

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8. Henderson, J.: On the Relationship of the Thymus to the Sexual Organs. I. The Influence of Castration on the Thymus, J. Physiol. **31**:222, 1904.

9. Jaffe, H. L.: The Influence of the Suprarenal Gland on the Thymus. I. Regeneration of the Thymus Following Double Suprarenalectomy in the Rat, J. Exper. Med. **40**:325, 1924.

10. Crowe, S. J., and Wislocki, G. B.: Experimental Observations on the Suprarenal Glands with Especial Reference to the Functions of Their Internal Portions, Bull. Johns Hopkins Hosp. **25**:287, 1914.

11. Jaffe, H. L.: The Influence of the Suprarenal Gland on the Thymus. II. Direct Evidence of Regeneration of the Involuted Thymus Following Double Suprarenalectomy in the Rat, J. Exper. Med. **40**:619, 1924.

sexually immature animals this stimulating influence manifests itself in further growth of the organ, while in older animals with highly involuted thymuses it brings about a regeneration or reviviscence of the gland. This regeneration includes both the medulla and the cortex, though it begins in the medulla. The medulla seems to act as a specialized type of germinal center somewhat analogous to the medulla of regenerating lymph nodes.

4. Gonadectomy combined with suprarenalectomy causes a still more marked regeneration than either of these influences operating alone. Their effect on the thymus, therefore, is complementary or augmentary. The gonadectomy influence is relatively weak and in our experience is capable only of delaying involution, while the effect of suprarenalectomy is very powerful, causing almost certain regeneration and permanently inhibiting involution if the suprarenal insufficiency is permanent.

5. Thyroidectomy prevents the regeneration of the thymus which usually follows suprarenalectomy. The fact has already been referred to that thyroidectomy alone brings about regression or involution of the thymus. In a series of twenty-seven rabbits with combined thyroidectomy and suprarenalectomy, seventeen had completely involuted thymuses, while in eighty-nine rabbits with suprarenalectomy alone, only twelve had involuted thymuses. A functionally active thyroid, therefore, appears necessary for the thymic regeneration which follows suprarenalectomy.

It requires little imagination to speculate on the possible relation of these experimental results to certain clinical associations in which the thymus is found enlarged, as for example, exophthalmic goiter, Addison's disease, acromegaly and status lymphaticus.

Marie,[12] in 1886, was probably the first to suspect regeneration or reviviscence, as he called it, of the thymus in exophthalmic goiter. The experiments here reported point strongly to the view that the thymus enlargement or regeneration so commonly seen in this disease, while occurring only in the presence of active thyroid tissue, is not primarily due to the increased thyroid activity as some have suggested, but rather to a primary lesion or insufficiency of some function of the interrenal gland. Indeed, as we have repeatedly pointed out, partial but sufficient suprarenal injury in the rabbit and cat leads to a transient syndrome almost identical with that seen in exophthalmic goiter.

The enlargement of the thymus seen in Addison's disease and in status lymphaticus also appears to be dependent on suprarenal insufficiency. Contrary to the views of other men prominently identified with

12. Marie, P.: Sur la reviviscence du thymus dans certaines affections presentant des alterations du corp thyroide ou de quelqu'autre vasculaire sanguine, Bull. et mém. Soc. méd. d. hôp. de Paris **10**:136, 1893.

this subject, like Paltauf,[13] Wiesel,[14] Hedinger [15] and others who believe the lymphoid overgrowth is due to a primary injury of the chromaffin tissue, we believe it is due to insufficiency of the cortex or the interrenal gland and gonads. The following facts support such a view: (1) The gonads exert an influence on the thymus which appears to differ only in degree from that exerted by the suprarenals. (2) Destruction of the suprarenal medulla or suppressing the excretion of epinephrin by division of the nerve supply of the remaining gland after the removal of one gland does not bring about thymus enlargement or regeneration. (3) In the rabbit, at least, involution of the regenerated thymus may begin when the accessory cortical or internal glands have regenerated sufficiently.

SUMMARY

Thyroidectomy hastens involution of the thymus.

Gonadectomy delays this involution but does not cause regeneration.

Suprarenalectomy not only delays involution of the thymus and lymphoid tissues, but actually causes their regeneration.

Thyroidectomy prevents this reaction even after combined suprarenalectomy and gonadectomy.

Suprarenalectomy plus gonadectomy is a more powerful stimulus for thymus and lymphoid regeneration than either of these influences alone.

The combined effect of these two factors results in certain lymphoid and thymus hyperplasia in rabbits and rats which persists until regeneration of accessory interrenal tissue corrects the physiologic defect.

The syndrome thus experimentally produced resembles status lymphaticus and is believed to depend mainly on a partial loss of certain functions in the interrenal and sex glands rather than of the chromaffin tissue.

The normal and abnormal lymphoid and thymic hyperplasias of infancy and childhood are believed to be manifestations of a functional underdevelopment of the interrenal and sex glands of varying intensity.

The so-called lymphatic constitution which underlies or accompanies exophthalmic goiter and Addison's disease also appears to be dependent on a partial suppression of certain functions of the interrenal and sex glands.

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13. Paltauf, A.: Ueber die Beziehungen der Thymus zum plötslichen Tod, Wien. klin. Wchnschr. **2**:877, 1889; **3**:172, 1890.

14. Wiesel, J.: Zur Pathologie des chromaffinen Systems, Virchows Arch. f. path. Anat. **176**:103, 1904.

15. Hedinger, E.: Ueber die Kombination von Morbus Addisonii mit Status lymphaticus, Frankfurt. Ztschr. f. Path. **1**:527, 1907.

COMPRESSION MYELITIS SECONDARY TO ECHINOCOCCUS DISEASE OF VERTEBRAE AND KIDNEY

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Echinococcus disease of the vertebrae is an extremely unusual cause of transverse myelitis. The rarity of the condition is emphasized by Williamson,[1] who, in 1911, was able to cite from the literature only twenty-four cases. Since 1911 there have been additional cases reported by Magath,[2] Guleke,[3] Davis and Balboni [4] and Fournier.[5]

According to a recent review by Kretschmer,[6] echinococcus disease of the kidney is also rare, and this report is based on the postmortem findings of echinococcus disease in both vertebrae and kidney.

REPORT OF A CASE

History.—A white woman, aged 38, a native of Ireland, was admitted to St. Joseph's Hospital, Chicago, Aug. 10, 1924, complaining of paralysis and severe pain of both lower extremities, marked constipation and polyuria. The illness started about June 1, 1924, with shooting pains in the right leg. This was followed by numbness and progressive weakness in both legs.

Examination.—The examination on admittance revealed a well nourished woman, acutely ill, with a temperature of 100.2 F. and a pulse rate of 126. The essential physical findings were: distention of the abdomen, bilateral flaccid paralysis of both lower extremities; loss of thermal, tactile and pressure sensation of both lower extremities and trunk below the twelfth dorsal segment; absent patellar, Achilles and abdominal reflexes. No pathologic reflexes were obtained. Blood culture and Wassermann tests of blood serum were negative. There were 19,100 leukocytes per cubic millimeter and 81 per cent. of polymorphonuclears. Urinalysis was negative on admission, but showed a trace of albumin and numerous pus cells the day before she died. Roentgenograms of the spine, spinal fluid examination and echinococcus complement-fixation tests were not made. Two days after admission she was unable to urinate or defecate voluntarily. A large sacral bed sore developed on the fourth day. The patient became very toxic, and died eleven days after admission.

Necropsy.—The anatomic findings at necropsy, made four hours after death, were: compression myelitis of the lower dorsal and upper lumbar cord; localized echinococcic pachymeningitis externa of the cord; multiple echinococcus

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1. Williamson, R. T.: Diseases of Spinal Cord, London, Oxford Press, 1911.
2. Magath, T. B.: Med. Clin. North America **34**:549, 1921.
3. Guleke, A.: Deutsch. Ztschr. f. Chir. **162**:59, 1921.
4. Davis, L., and Balboni, G. M.: Boston M. & S. J. **176**:726, 1917.
5. Fournier, J. C. M.: Rev. de med. del Uruguay **21**:523, 1918; abstr., J. A. M. A. **71**:203, 1918.
6. Kretschmer, H. L.: Surg., Gynec. & Obst. **36**:196, 1923.

cysts of the eleventh and twelfth dorsal and first lumbar vertebrae; large sterile (?) echinococcus cyst of the right kidney; sacral decubitus ulcer; cloudy swelling of the liver, myocardium and kidneys; chronic passive congestion of the spleen; passive hyperemia of the lungs; distended and trabeculated urinary bladder; old surgical ablation of the gallbladder; fibromyoma of the uterus; simple cyst of the left ovary and pelvic adhesions.

A large cyst, 12 by 9 by 9.5 cm., protruded from the anterior surface of the lower pole of the right kidney. One surface was partially embedded in the cortex of the kidney; the lower border was about 5 cm. below the lower pole. The cyst contained about 200 c.c. of slightly turbid brown fluid. The walls were 4 mm. thick and lamellated. The lining of the cyst cavity was generally smooth, except for a few brown, granular areas and small domelike projections. No hooklets or scolices were found in the fluid content, in the smears from the lining or in microscopic sections from the wall. The bodies of the eleventh and twelfth dorsal and first lumbar vertebrae were so friable that they could be broken easily. This was due to marked sponginess or cystic changes in the bone. In the loose tissue between the dura mater of the cord and the affected vertebral bodies, a light yellow exudate was expressed, which contained a few small gelatinous cysts. Smears revealed occasional scolices and numerous hooklets. Sectioned surfaces of the cord were grossly unchanged.

COMMENT

The comparatively large size of the kidney cyst and absence of daughter cysts in the contents indicate that the kidney was infected for a long time and was probably the primary site of infection. The small cysts in the vertebrae and around the cord suggest recent involvement, and this coincides with the short period of clinical evidence of cord compression.

Development of cysts outside the dura mater is the usual method of spinal compression. Williamson points out that it is exceptional to find cysts within the dura mater.

Any part of the cord may be involved. In Williamson's twenty-four cases, the cervical cord was involved in 2; the dorsal in 10; the lumbar in 6; the cauda equina in 5 and the dorsal, lumbar and cauda equina in 1. In this same series the site of origin was: cancellous tissue of vertebrae, 7; extradural areolar tissue, 4; arachnoid tissue, 2; muscles of back, 4; lung, 2; retroperitoneal tissue, 2.

SUMMARY

A case of echinococcus disease is reported in which the spinal cord was compressed by hydatid cysts that developed outside the dura mater. Recent cystic changes in the vertebrae and an old echinococcus cyst of the kidney were associated findings.

WINTERGREEN POISONING *

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AND

JOHN D. NOURSE, M.D.

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It does not seem to be generally recognized that methyl salicylate in moderate amounts is a powerful poison. While deaths due to this drug have never resulted from its therapeutic use, instances of untoward effects following accidental or intentional self-administration have been reported. Unfortunately, however, the great majority of these reports are clinical in nature. To date, only a single account of wintergreen poisoning has been published that contains the results of postmortem examination. We therefore report a case which has certain unusual features, together with a concise summary of the material on this subject obtained from the literature.

The fact that the salicylates are intimately related to the phenols was sufficient to draw attention to the possible toxic properties of these compounds. In this regard the methyl ester has always been held in greater respect than the sodium salt, as a consequence of which the latter came to be much more frequently employed in treatment than the oil of wintergreen. Subsequent investigation [1] has borne out the validity of this tradition, and has shown that the toxicity of methyl salicylate may be ascribed in part to its comparatively greater lipoidal solubility and in part to the fact that it suffers less destruction within the body after its absorption. Thus, for instance, we were able to demonstrate satisfactorily the presence of the unchanged oil in the urine of our patient about thirty hours after ingestion of the drug.

LITERATURE

Altogether, five clinical reports of deaths ascribed to methyl salicylate intoxication have been published. Six other reports of severe poisoning with complete recovery have also appeared. Several of the latter contain descriptions of symptoms that may have been due to definite pathologic changes similar to those found in the case we report. Pinkham [2] has made the only satisfactory study of the pathology of this type of poisoning in man. Table 1 presents in summary the significant

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* From the Department of Pediatrics, Western Reserve University Medical School, and Lakeside Hospital, Cleveland.

1. Hanzlik, P. J., and Wetzel, N. C.: J. Pharmacol. & Exper. Therap. **14**:43, 1920.

facts in the literature. For the sake of comparison the more important data on poisoning from sodium salicylate have been included in Table 2. The reports of fatal cases with necropsies are abstracted as follows:

Pinkham[2] describes the first case.

Clinical.—A young married woman had taken 30 c.c. of oil of wintergreen in order to produce abortion. Headache, perspiration, gastric distress, emesis

TABLE 1.—*Methyl Salicylate Poisoning*

Authors	Age of Patient	Sex*	Amount Ingested, C.c.	Appearance of Symptoms after Ingestion, Hours	Outcome	Remarks
Gallaher (Phil. M. Examiner **8**: 347, 1892)	9	♂	15	"Early"	Recovery	Inordinate appetite and thirst; no delirium; calomel and bloodletting
Jewett (New York M. Gaz. **1**: 380, 1867)	55	♀	45	"Early"	Death	Failure of sight and hearing
Hamilton (New York M. J. **21**: 602, 1875)	..	..	15	1	Recovery	Contracted pupils; tremors of whole body; hemiparesis of left side; mania; improved in two weeks
Beck (M. Jurispr. **2**: 492)	(Six soldiers)	..	..	..	Recovery	Accidental poisoning by wintergreen tea; vertigo, weakness and vomiting
Stille (Materia Med., p. 506)	9	♂	15	..	Recovery	Severe vomiting and purging; rapid pulse, slow and labored respirations; tinnitus; uncontrolled desire for food
U. S. Dispensatory (reported by Hamilton)	..	..	30	..	Death	
Pinkham (Boston M. & S. J. **117**: 548, 1887)	25	♀	30	15	Death	Convulsions and tonic spasms before death; kidneys congested; brain normal
McNerthney (Northwest Med. **1**: 405, 1903)	3	♂	12	3	Death	Opisthotonus with twitching limbs
Baum (Clin. Ophth., 1904, No. 3)	..	..	"Large"	..	Recovery	Amblyopia for 5 days
Rosenbloom (J. A. M. A. **72**: 22, 1919)	40	♂	30	½	Recovery	Nervousness, excitability, diarrhea, tinnitus, fever; acetone and diacetic acid for 12 days; hypodermoclysis and venesection
Myers (J. A. M. A. **75**: 1788, 1920)	2	♂	30	1	Recovery	Drowsiness and air hunger; acetone and diacetic acid in urine; respirations ceased at 48 hours, restored artificially; uneventful recovery
Legrain and Badonnel (Paris Letter, J. A. M. A. **78**: 1140, 1922)	35	♀	60	10	Death	Epileptiform convulsions; cyanosis and collapse; lavage within 15 minutes returned most of the drug

and purging followed rapidly. Sight and hearing were abolished. She developed general convulsions, with tonic spasms of the hands and feet. Within fifteen hours of taking the potion she died in collapse.

Necropsy.—This revealed: marked congestion of the mucosa of the intestinal tract and congestion of the kidneys, but no changes in the brain. There were no internal hemorrhages. (This is noteworthy in view of the fact that the clinical course was marked by convulsions.)

2. Pinkham, J. G.: Boston M. & S. J. **117**:548, 1887.

Legrain and Badonnel[3] report the only other case of wintergreen poisoning with postmortem examination.

Clinical.—A woman had taken 60 c.c. of the oil with the intention of committing suicide. Gastric lavage within fifteen minutes of ingestion returned almost all of the drug. Emesis was induced with linden flower infusion. The vomitus had a strong odor of wintergreen. Ten and one-half hours after the ingestion she complained for the first time of weakness and nausea. Epileptiform convulsions followed, the patient passing into a state of deep coma, marked by occasional twitching of the extremities. Cyanosis increased, and she died eighteen hours after swallowing the oil.

Necropsy.—This revealed insufficiency of the liver and of the kidneys. Nothing was said of the condition of the brain.

Quincke[4] made a thorough study of his case of sodium salicylate poisoning.

Clinical.—A girl, aged 17, suffering from chronic rheumatism, had received a total of 34 gm. of sodium salicylate in the course of three days. She seemed

TABLE 2.—*Sodium Salicylate Poisoning*

Authors	Age of Patient	Sex*	Amount Ingested, Gm.	Appearance of Symptoms after Ingestion, Hours	Outcome	Remarks
Quincke (Berl. klin. Wchnschr. **19**:709, 1882)	17	♀	34	72	Death	Treated for chronic rheumatism
Gibson and Felkin (Practitioner **42**:17, 1889)	40	♀	20	8	Recovery	Myosis with loss of pupillary reflex, recovery in 30 hours; reappearance a few days later with two doses of 20 grains
Mann (Med. Rec. **41**: 181, 1892)	40	♂	4	"Early"	Recovery	Hallucinations with delusions of persecution; recovery after 5 days; had subacute rheumatism
Langmead (Lancet **1**: 1862, 1906)	5	♂	100	..	Death	Symptoms after 10 weeks' treatment for rheumatic endocarditis; daily dose, 20 grains
Langmead	4	♀	300	..	Death	Coma and air hunger; therapy for 3 days

to improve under this treatment. The pupils became dilated and did not react to light, whereupon the administration of the drug was stopped. Deep and labored breathing soon set in and she died in spite of stimulation.

Necropsy.—The longitudinal sinus contained fluid and clotted blood. All the vessels were deeply injected. There were numerous punctuate hemorrhages in the brain and many areas of ecchymosis beneath the epicardium. The musculature of the heart was pale. The kidneys were hyperemic. Quincke calls particular attention to the fact that these changes are also found in experimental poisoning in animals.

REPORT OF AUTHOR'S CASE

History.—Thirty hours before admission a previously healthy infant, 21 months old, drank about 10 c.c. of the pure oil of wintergreen. A physician

3. Legrain and Badonnel: Paris Letter, J. A. M. A. **78**:1140, 1922.
4. Quincke, H.: Berl. klin. Wchnschr. **19**:709, 1882.

had administered an unknown antidote but did not wash the stomach. Vomiting appeared within four hours of the accident, and from this time on the child retained nothing that was given by mouth. Meanwhile, he became drowsy, and, on failing to recognize his mother, he was brought to the hospital for treatment.

Examination.—The patient was an extremely well developed child in a state of coma. The skin was hot and flushed, and cyanosis of the lips and finger tips was evident. The respirations were rapid and deep, and there was a distinct odor of acetone in the expired air. An occasional convulsive shudder shook the entire body. This seemed to be somewhat more marked on the right side. The scalp showed no evidence of injury. At first, the pupils were moderately dilated, but they reacted promptly and equally to light. Later, they became markedly constricted, remaining in this condition for several hours, after which they again became dilated. The fundus examination was negative, the absence of hemorrhages being carefully noted. No lesions were present in the mouth. The heart and lungs were normal, although there was a moderate elevation of both the pulse and respiratory rates. The pulse was regular, and on palpation showed a well marked stroke volume. The abdomen was likewise normal. The knee and ankle reflexes were bilaterally equal but hyperactive. Babinski's sign was easily obtained on both sides. Kernig's sign could not be elicited. The superficial reflexes were present and bilaterally equal. Sensory examination was impossible because of the state of coma.

The urine contained a faint trace of albumin, no sugar, but gave good reactions for acetone, salicylate radical and free methyl salicylate. There were occasional hyaline casts.

Course.—The milder sedatives, such as calcium and sodium bromid, did not quiet the patient. Morphin sulphate, $\frac{1}{12}$ grain (0.005 gm.), hypodermically, also failed to suppress the convulsive seizures. Within five hours of admission, evidences of pulmonary edema suddenly appeared, and the child died thirty-six hours after ingestion of the drug.

Postmortem Examination.—For the sake of brevity, negative findings are not included.

The mesenteric vessels were moderately dilated, which was particularly well seen in the walls of the intestine. Beneath the pleural surfaces of both lungs were numerous small irregular hemorrhages, which, on section, were found to extend deeply into the lung tissue. The cut surface of the lung was mottled with many dark red, hemorrhagic areas. Considerable bloody and frothy fluid could be expressed. Crepitation, however, was felt throughout the entire lung tissue. Numerous small subepicardial hemorrhages were present in the heart. The cut surface of the liver presented a cooked appearance, being light brownish yellow. Lobular markings could not be distinguished. The spleen was slightly enlarged and firm. The corpuscles stood out prominently. The kidneys were much more pale than normal, especially in the cortical regions where the striations could not be seen. The pyramids, however, were well defined. A small area of postmortem digestion was found near the fundus of the stomach. There was no odor of wintergreen. The remainder of the gastro-intestinal mucosa was quite normal, but all the lymphoid follicles in the ileum were hyperplastic, particularly in the region of the ileocecal junction. Follicular hyperplasia in the colon was slight.

On reflecting the scalp, a small localized hemorrhage 1.5 cm. in diameter was found in the deep tissue over the occipital protuberance about 1 cm. to

the right of the midline. This hemorrhage extended down to the epicranium. Another hemorrhage about 2 cm. in diameter was similarly located in the left frontal region. It will be recalled that external evidence of these hemorrhages was entirely lacking. The calvarium was easily removed, disclosing beneath the dura a massive blood clot extending over the entire left cerebral hemisphere. This clot was adherent to the dura, being completely removed on turning back the dura. There was no hemorrhage of the pia-arachnoid. The vessels of the surface of the brain, particularly on the left side, showed only moderate engorgement. No gross lesion of the brain could be found. Suture lines were well united, but the anterior fontanel was open, measuring 2.5 by 1 cm. Careful search failed to reveal a fracture of either table of the skull.

Microscopically, the liver showed generalized fatty changes and cloudy swelling; there was cloudy swelling and fatty degeneration in the tubular portion of the renal cortex, but the glomeruli were free from change. There was, however, a generalized hyperemia of the kidney parenchyma. The lungs were congested; in several areas there were recent hemorrhages. There was moderate hyperplasia of the splenic pulp and lymph nodes. The dura was normal in structure.

COMMENT

In reviewing the cases so far reported, it is clear that poisoning from methyl salicylate produces profound physiologic and pathologic changes, which differ, perhaps only in degree, from those of ordinary salicylism. In the first place, the most frequent as well as the most alarming clinical evidences of poisoning are the symptoms referable to stimulation of the central nervous system. All the fatal cases have presented certain major nervous symptoms, such as convulsions, clonic or tonic spasms of the extremities and even hemiplegia. Any of these may have resulted from the direct central action of the drug; yet, after considering the great similarity of the findings in our own case to those recorded by Quincke, it seems probable that small parenchymatous hemorrhages of the brain, or even a larger and more diffuse meningeal or basilar hemorrhage, may have been indirectly concerned with the cause of these symptoms.

While it may also appear that the unusually extensive hemorrhage herein described was merely a coincidental event, because the necropsy revealed the presence of smaller extravasations below the aponeurosis of the occipitofrontalis, it is perhaps more likely that all of these hemorrhages as well as those in the lungs and in the kidneys were the direct result of severe and permanent injury to the vascular system. Trauma, as an etiologic factor, was excluded on the basis of careful inquiry into the history, and because no evidence of it existed in either the clinical or in the postmortem examinations. The numerous ecchymoses noted by Quincke and the extensive extravasation which we report afford ample evidence that salicylate poisoning is characterized by general vascular depression.

In certain respects, the massive subdural hemorrhage was similar to that found in internal hemorrhagic pachymeningitis. This is of interest

as the etiology of that disease is still obscure. It should be noted, however, that retinal hemorrhages, which occur in about 75 per cent. of the cases of pachymeningitis, were not seen in our case of poisoning. Had our patient survived, it is reasonable to assume that the process of healing might have produced a result comparable to the lesions of that disorder.

Another prominent feature of methyl salicylate poisoning which has occurred in the majority of cases is the profound alteration in metabolism accompanied by a state of ketosis. This condition is characterized clinically by the diabetic type of respiration without glycosuria, and by the presence of acetone in the breath and in the urine. In addition, diacetic acid is also commonly found.

The evidence at hand, therefore, tends to show that the internal administration of methyl salicylate is not a harmless procedure. For this purpose it is far more desirable to prescribe salicylate in the form of the sodium salt, combined with equal amounts of sodium bicarbonate to alleviate possible gastric distress that might follow the liberation of free salicylic acid in the stomach. The therapeutic use of methyl salicylate, accordingly, should be confined to external administration in the form of a liniment or an ointment. Sollmann [5] believes that this method of administration is apt to be more effective than when the drug is given internally.

The treatment of methyl salicylate poisoning has been remarkably ineffective. Deaths have occurred in spite of repeated attempts to remove the drug either by lavage of the stomach or by catharsis. Violent attacks of vomiting following ingestion have also failed to remove sufficient amounts to prevent untoward results. Under these conditions, it must be clear that relatively small quantities of the drug have been the cause of death, and that prevention is imperative. Gastric lavage with warm 1 per cent. sodium bicarbonate has been used, and it seems to be the most logical solution for this purpose. Success depends much on the other factors of time and of the amount already absorbed, so that not too much hope can be placed on this procedure. Supportive treatment during the stage of collapse and sedatives during the period of stimulation seem to be indicated. Insulin, in small amounts, might be employed to combat the ketosis.

Access to oil of wintergreen should be made impossible for children and for persons ignorant of its poisonous properties. A further danger exists in the form of the extract and the spirit of wintergreen, both of which may be in demand because of their alcoholic content.

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5. Sollmann, T.: A Manual of Pharmacology, ed. 2, Philadelphia, 1922.

SUMMARY

The clinical and pathologic features of poisoning due to oil of wintergreen have been described in connection with a complete review of all the cases so far reported.

Fatal poisoning may be produced by relatively small amounts of methyl salicylate. Absorption of less than 15 c.c. has repeatedly resulted in death.

Vascular changes are the most prominent among the effects. Multiple subserous hemorrhages of the heart, lungs, and meninges, and parenchymatous hemorrhages of the brain, lungs and kidneys are produced. An unusually extensive subdural hemorrhage occurred in the present case.

Particular caution should be exercised to prevent the indiscriminate use of pharmaceutical preparations containing the oil of wintergreen.

LEUKOCYTIC REACTIONS IN SMALLPOX, CHICKENPOX, SCARLET FEVER, MEASLES AND MUMPS*

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Some years ago when one of us desired the leukocytic formulas of the various acute infectious diseases, he was much disappointed with the results obtained on a general search of available medical literature. Isolated counts could be found, but they were usually reported without reference to the clinical stage of the disease process; the change in picture from day to day during the disease was hardly to be found. This led to a study of the blood picture in the acute infectious diseases occurring in the student clinic and infirmary of the University of Wisconsin during various epidemics and in isolated cases. A considerable amount of material has thus accumulated, and from this there have already been published the data obtained in influenza [1] of the 1920 epidemic and the findings in acute infectious jaundice.[2] Reports of the leukocytic reactions in acute infectious mononucleosis (glandular fever?) are in preparation.

It has seemed that it might be of value to put on record type reactions in the other epidemic diseases that have been studied, with such comments as may be deemed necessary, but without devoting a separate article to each disease. We are therefore presenting the leukocytic pictures seen in smallpox, chickenpox, measles, mumps and scarlet fever. In considering the counts, it is to be remembered that they represent the reaction of young adults of university age to the various infections. We have no evidence that at this age there is any qualitative difference in reaction from that at any other age, nor have we direct evidence of quantitative variations, although from reactions in certain chronic diseases its possibility is not to be denied.

Daily total and differential leukocyte counts have been made in each disease so as to follow the leukocytic picture throughout. The counts have been made and the smears taken at the same time of day in each case, as far as possible, so as to avoid changes that might be due to the diurnal variation which occurs in the human subject. Early in our work it was found that the afternoon count of leukocytes might exceed the

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* From the Pathological Laboratory and the Student Infirmary, University of Wisconsin.

1. Bunting, C. H.: Am. J. Med. Sc. **162**:1, 1921.
2. Thewlis, E., and Middleton, W. S.: Am. J. Med. Sc. **169**:59, 1925.

early morning count by as much as 2,000 cells without any marked alteration in the differential picture. In the differential counts, the leukocytes have been grouped into seven classes, as advocated by one of us (C. H. B.).[3] A word of explanation is necessary concerning some of these groups; however, not concerning the first three, which consist of the well-known marrow cells, the neutrophilic, eosinophilic and basophilic granular cells with polymorphous nucleus. The lymphocytes have been classified as small and large. No description is needed of the small lymphocyte. The large lymphocyte enumerated in this paper is, however, not a cell found in normal blood, but is apparently a cell more primitive than the small lymphocyte and lying between it and the lymphoblast in the matter of size, as well as in genealogic relationship (Bunting[4]). This cell has a nucleus somewhat larger than that of the small lymphocyte and has a moderate rim of basophilic protoplasm, so that in size it approaches the neutrophil leukocyte. It is present in normal lymphoid tissue, but apparently escapes into the blood stream only in rather intense lymph-gland reactions. It constitutes quite a percentage of the cells in the more acute lymphatic leukemias and in infectious mononucleosis; also, as will be seen, in some of the infections to be recorded.

In regard to the division of the large cells, the monocytes, into large mononuclears and transitionals, it may be said that it is scarcely necessary to make the distinction in normal blood if the large mononuclear is but an immature transitional (Bunting, Sabin[5]), yet in pathologic blood an increased proportion of the immature forms may indicate a reaction of increased intensity. While the origin of these cells in normal blood is still unsettled, we have considered them to be of marrow origin. In certain pathologic conditions, cells of practically the same type of lymphoid tissue origin occur in the blood stream, and are distinguishable from the normal monocyte with difficulty if at times at all. The lymph node monocytes are commonly smaller, and have a more hyaline protoplasm than those from the bone marrow.

With these explanations, we may offer our findings in the diseases in question. We desire in presenting them to express our thanks to Dr. W. S. Middleton for the careful clinical observations in all the cases studied.

SCARLET FEVER

We present the leukocytic picture of scarlet fever first for two reasons: first, because since these counts were made, the cause of the

3. Bunting, C. H.: Bull. Johns Hopkins Hosp. **22**:369, 1911.
4. Bunting, C. H.: Physiol. Rev. **2**:505, 1922.
5. Sabin: Bull. Johns Hopkins Hosp. **34**:277, 1923.

disease has been discovered, and we thus have a basis for interpreting the picture; and, second, because at first glance the counts appear to differ from those in other diseases followed by immunity. The count in the selected case is given in table 1.

There is, as may be noted, a maximum neutrophil leukocytosis on the day of the appearance of the rash, with a steady but gradual diminution of the total count and the total number of neutrophils during the course of the disease. This characteristic has appeared in all the cases studied. The highest initial percentage of neutrophils found was 91.4, although the total number was slightly lower than in the case reported. Unfortunately, we were unable to obtain the development of this leukocytosis during the prodomal period.

The eosinophils have shown in this, as in our other cases, a rather sharp rise in both percentage and total number. The maximum per-

TABLE 1.—*Blood Cell Count in Selected Case of Scarlet Fever*

		Neutrophils		Eosinophils		Basophils		Small Lymphocytes		Large Lymphocytes		Large Mononuclears		Transitionals	
1920	Total	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
3/15	28,200	89.6	25,267	2.2	620	0.0	00	3.4	959	1.0	282	0.4	112	3.4	960
3/16	19,800	83.5	16,533	3.5	693	0.5	99	3.0	594	1.5	297	0.0	40	8.0	1,584
3/17	21,200	79.0	16,748	5.2	1,102	0.0	00	6.0	1,272	0.2	42	0.2	42	9.4	1,993
3/18	23,100	78.0	18,018	6.2	1,452	0.2	46	6.4	1,478	1.2	277	0.0	00	8.0	1,848
3/19	19,200	67.5	12,960	6.5	1,248	0.0	00	11.5	2,208	1.5	288	0.0	00	13	2,496
3/20	15,000	59.5	8,925	6.0	900	0.5	75	14	2,100	0.0	00	0.5	75	19.5	2,925
3/21	17,600	52.8	9,296	6.2	1,091	0.2	35	24.0	4,224	2.6	457	0.2	35	14	2,464

Clinical Data: The patient was admitted to the hospital on March 15 with a scarlatinal, maculopapular eruption over the chest and abdomen and with a typical throat and prominent papillae on the tongue. The temperature varied from 101.4 to 102.2 F. There was a gradual fading of the rash and a fall of temperature to normal on March 20. Branny desquamation was first noted on March 20.

centage reached in the cases studied was 8.6, although the total number did not equal that found in this case. The cells were still high in number in one case thirteen days after the appearance of the rash.

The basophil cells appear to be uninfluenced by the infection.

The lymphocyte curve in this case appears also to be typical. There is noted an early sharp fall in percentage and total number with a gradual recovery and a peak reached at about the end of the first week of the disease.

As may be noted, the monocyte curve parallels rather closely the lymphocyte curve, with an increasing percentage and total number, although the total leukocyte count falls.

Interpretation.—The neutrophil increase is apparently to be interpreted as the reaction of the body to the invasion of a mucous membrane by a living organism. The excessive leukocytosis here over that in the other diseases described in the following is probably due to the fact that the etiologic agent belongs to the group of pyogenic streptococci. The

eosinophil reaction is probably due chiefly to the skin injury in scarlet fever, and possibly to some extent to the involvement of the pharyngeal mucous membrane. The lymphoid reaction we feel is concerned with the subsequent appearance in the blood stream of immune bodies (antitoxin), as shown in the recent scarlet fever investigations. The picture in scarlet fever is, however, not unequivocal for that conclusion, as there occurs an almost simultaneous reaction on the part of the monocytes, and they cannot therefore be excluded as a possible factor in producing

TABLE 2.—*Typical Case of Smallpox in 1921 Epidemic*

		Neutrophils		Eosinophils		Basophils		Small Lymphocytes		Large Lymphocytes		Large Mononuclears		Transitionals	
1921	Total	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
3/13	8,400	....	.....	...	..	...	..	....	...	...	...	...	..	...	...
3/14	6,200	81.5	5,053	0.5	31	0.0	00	12.5	775	2.5	155	0.5	31	2.5	155
3/15	6,200	48	2,976	2.5	155	0.0	00	30	1,860	8	496	5.5	341	6	372
3/16	6,400	28.5	1,824	0.5	32	0.0	00	45	2,880	14	896	6	384	6	384
3/17	11,600	30	3,480	0.0	00	0.0	00	40	4,640	18.5	2,146	6	696	5.5	638
3/18	19,800	24	4,752	0.5	99	0.0	00	49	9,708	16	3,168	3.5	693	7	1,386
3/19	20,000	27.5	5,500	0.5	100	0.5	100	64.5	12,900	5	1,000	0.5	100	1.5	300
3/20	13,200	33.5	4,422	1	132	0.5	66	57	7,524	4.5	594	0.5	66	3	396
3/21	24,000	25	6,000	1	240	0.5	120	60.5	14,520	9.5	2,280	0.5	120	3	720
3/22	16,400	21	3,444	0.5	82	0.5	82	64	10,496	8.5	1,394	0.0	00	5.5	902
3/23	19,600	21.5	4,214	1	196	1.5	294	59	11,564	9.5	1,862	2.0	392	5.5	1,078
3/24	19,800	22	4,066	0.5	99	0.5	99	63	12,474	6.5	1,287	2	396	5.5	1,089
3/25	18,800	24	4,512	0.0	00	1.5	282	63.5	11,938	7	1,316	1.5	282	2.5	470
3/26	15,800	30	4,740	1.0	158	0.5	79	59	9,322	6.5	1,027	1	158	2	316
3/27	16,000	34.5	5,510	1.5	240	0.0	00	57	9,120	4.5	720	1	160	1.5	240
3/28	14,000	27	3,780	1	140	0.5	70	62.5	8,750	6	840	0.5	70	2.5	350
3/29	15,200	26.5	4,028	1.5	228	1.5	228	58	8,816	6.5	988	1.5	228	4.5	684
3/30	12,000	33.5	4,020	2.0	240	0.0	00	55	6,600	4	480	0.5	60	5	600
3/31	10,400	38	3,952	0.0	00	0.5	52	54	5,616	3	312	0.5	52	4	416

Clinical Data: The patient had a prodromal erythematous rash four days before admission on March 13. For two days she had backache and malaise. On admission there was a blotchy macular eruption over the whole body. The temperature was 106 F.

On March 14, there was an erysipelatous, purplish elevated lesion over the forehead, over the bridge of the nose and on the cheeks. Macular blotches persisted over the body with a punctate eruption on the back. There were several areas of petechial hemorrhage. The temperature was 104.4 F.

On March 15, some vesicles appeared on the face and a few papules on the arms.

On March 16, there was a fading erythematous rash with more papules and vesicles.

On March 17, a few pustules with extreme and papular eruption appeared on the face and extremities.

On March 18, there was extreme confluent pustulation of the face; innumerable papules and pustules appeared on the arms, legs, palms and soles. The temperature was 101.6 F.

On March 20, there was a marked edema of the face; pustules, extreme.

On March 21, umbilicating and crusting of pustules occurred.

On March 24, there was progressive healing and crusting. The temperature was normal.

On March 30, the lesions were gradually drying.

the result. The disease picture seems to indicate definitely, however, that the reaction to living organisms is through neutrophil response and to toxins through lymphoid or mononuclear response.

SMALLPOX

The smallpox cases studied occurred in a relatively mild epidemic among the student body in the early part of the year 1921. A confluent case is presented as being somewhat emphatically typical of the picture seen. No case of the rapidly fatal malignant or hemorrhagic smallpox was seen in the epidemic.

Summary.—There is an early diminution in the total count leading to a leukopenia of variable degree; it was moderate in the case reported. Ten of our sixteen cases gave counts of 5,000 or less, and the minimum count was 2,600 cells. This leukopenia is usually well marked before the appearance of any skin eruption, and may be noted at least three days before in a high percentage of cases. It usually persists for two days after the skin eruption is noted, and may persist for four days. It is then followed by a rather sharp rise to a well marked leukocytosis, which persists irregularly during the active stage of the disease. In milder cases this leukocytosis was not as marked as in the reported case. The lowest maximum leukocytosis of the cases studied throughout was 10,600; the highest maximum, 24,000 in the reported case.

There is early a relative and absolute increase in neutrophils, followed by a rapid diminution in both percentage and absolute number to a point below normal. With the development of leukocytosis, the percentage remains consistently low, but the total number is close to normal, either slightly above or slightly below.

In this case the eosinophils show a consistently low percentage, although they have risen above the total normal number per cubic millimeter on several occasions during the course of the disease. In the cases studied this has been fairly generally true, although in cases with less sharp leukocytosis the percentage may be higher than in this type of case without indicating any greater increase in the total number of cells in the unit of blood.

The basophils show no striking or consistent curve.

After an early reduction in percentage and number of lymphoid cells, there is a sharp rise in both, until at the height of the leukocytosis small and large lymphocytes together constituted 70 per cent. of the total 24,000 cells. There is great variation in the size of the lymphoid cells, making classification difficult.

The monocytes, after an early slight depression, are moderately increased in percentage and number.

There appeared in this case on March 15, 16 and 17, cells, included among the large mononuclears in the count, which have been interpreted as capillary endothelial cells. They exceeded the transitionals in size, had a sharply outlined large spherical or occasionally oval nucleus, with nucleolus, and a large amount of deeply basophilic protoplasm without specific granulation. From 1 to 2 per cent of these cells have been almost constantly present in the early days in the smallpox cases studied, also in chickenpox and in measles. In one smallpox case one such cell was seen in mitosis.

Neutrophilic myelocytes have not been a constant finding in the cases studied; in fact, they were recorded in only a single case of smallpox.

In three cases of smallpox, seen early, there have been found bodies in the large lymphocytes unlike anything seen in a relatively long experience with blood smears. One type of body was protoplasmic, was of practically the size of the nucleus and stained an unusual light clear blue with the Wright stain used. The blue in its tint suggested the mucus reaction with hematoxylin. In addition to these bodies, small metachromatic (reddish) granules, often with an apparent vacuole about them, were found in the nuclei of large lymphoid cells.

Interpretation.—A study of the cellular content of the smallpox pustule is illuminating in an attempt to interpret the blood picture. The pustules are rich in all types of blood cells, but especially so in neutrophils and eosinophils, but with abundant lymphoid elements and basophils. There is apparently no inhibition of marrow activity in smallpox, but instead a great outpouring of cells and a great withdrawal of cells from the circulation to the skin lesions. One gets no idea of the mass of this production from the percentage or total number of eosinophils in the circulation, for example, as the count indicates merely the ratio between supply and demand, and here demand has almost equaled supply. The curve in smallpox shows that an unusually sharp lymphoid reaction takes place. The blood picture at the height of this reaction resembles that in infectious mononucleosis, or even of an early acute lymphoid leukemia. There is almost every size of cell, from the lymphoblast to the smallest lymphocyte, with high percentages of the intermediate or large lymphoid cells. The interpretation of the large cells described as capillary endothelial cells seems justified to us. We first noted them in measles, in which Mallory and Medlar [6] have demonstrated an unusual proliferative activity in the capillary endothelium of the skin. Whether their appearance in the blood is to be related to proliferation in this organ or in others is undetermined, yet they seem to appear in those diseases with a macular skin rash. We have noted them in one case of secondary syphilis when the skin rash was present.

We have been inclined to identify the unusual bodies found in the large lymphoid cells as the so-called "Councilman" bodies found in the cells of other tissues in smallpox. They are, at least in our experience, peculiar to the disease.

CHICKENPOX

Comment.—The blood curve in chickenpox, as may be noted, follows the general picture seen in smallpox qualitatively, but quantitatively the range of cellular variation is in general smaller. It may be compared to a mild case of smallpox with limited skin lesions.

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6. Mallory and Medlar: J. M. Res. **41**:327, 1920.

MEASLES

Summary.—With the appearance of the rash the blood showed a leukopenia of varying degree and of several days' duration. In two of our series in this primary leukopenia, the count was 2,600, in another 2,800, and in still another 3,000. The leukopenia may be of a week's duration. Following it there is a gradual rise to a number of cells, but slightly above the normal count. The maximum count in our series has not exceeded 12,000, except in one case in which there was a count of 16,000 on the ninth day of the disease.

With the falling total count at the onset of the disease, there is a percentage rise of neutrophils, but not an increase in the total number.

TABLE 3.—*Blood Cell Count in a Case of Chickenpox*

		Neutrophils		Eosinophils		Basophils		Small Lymphocytes		Large Lymphocytes		Large Mononuclears		Transitionals	
1922	Total	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
10/25	4,200	67	2,814	1.5	63	2.0	84	11.5	483	5	210	2	84	11	462
10/26	3,800	50.5	1,919	0.0	00	0.5	19	17	646	9	342	7	266	16	608
10/27	8,600	32	2,752	1.5	129	0.0	00	34.5	2,709	21	1,806	3	258	7.5	645
10/28	7,600	27.5	2,090	1	76	0.5	38	44.5	3,382	20	1,520	1	76	5.5	418
10/29	7,600	41	3,116	1.5	114	0.5	38	34.5	2,622	14	1,064	2	152	6.5	494
10/30	7,400	56.5	4,181	7	518	0.5	37	24.5	1,813	5.5	407	0.0	00	6	444
10/31	8,000	64	5,120	5.4	432	0.0	00	17.5	1,200	4	320	1	80	8	640
11/ 1	9,000	54	4,860	7	630	0.0	00	24.5	2,205	7	630	0.5	45	7	630
11/ 2	7,800	53.5	4,173	3.5	273	1	78	32	2,496	3	234	0.5	39	6.5	507
11/ 3	11,000	57.5	6,325	4.5	490	1	110	24	2,640	5	550	0.5	55	7.5	825
11/ 4	8,400	58.5	4,914	5.5	462	1.5	126	24	2,016	3.5	294	0.5	42	8.5	798
11/ 5	.....	....	.....	...	...	...	...	....	.....	...	...	...	..	...	...
11/ 6	11,000	54.5	5,995	5	550	2.5	275	27	2,970	2.5	275	1	110	8	880
11/ 7	8,800	64	5,632	4	352	0.5	44	26.5	2,332	5	440	0.5	44	4.5	396
11/ 8	14,000	64.5	9,030	4.5	630	3	420	18.5	2,590	5	700	0.5	70	4	560
11/ 9	10,200	67.5	6,885	3.5	357	0.5	51	22.5	2,295	0.5	51	0.0	00	5.5	561

Clinical Data: There was a history of onset on October 21 with headache. There was backache and malaise on October 22. She was admitted to the hospital on October 24, with an eruption mainly in the papular stage on the back and trunk. On October 25, a fresh crop of papules and vesicles appeared on the face and body. The throat was congested; the temperature varied from 101 to 102 F. The patient was afebrile on October 29. The last crusts disappeared from the lesions on November 9.

This is followed by a rapid decrease in both percentage and total number. Our minimum total number in the patients studied was 25.5 per cent in a total count of 3,400. Following this depression, there is a gradual rise in both percentage and total number during the second week of the disease.

There is a tendency to a moderate eosinophilia. The degree of this depends somewhat on the reactional ability of the patient as far as this particular bone-marrow element is concerned. There may be an early depression of number followed by a gradual rise or, as in the count in table 4, there may be an excessive percentage from the onset.

The basophils remain apparently at or near the normal percentage.

There is apparently an initial lymphopenia depending for its degree and duration somewhat on the intensity of the infection. In the count reported it is scarcely to be noted, if one includes both large and small

lymphocytes. Our most extreme case showed but 6.4 per cent of 6,000 cells on the second day of the rash. In general, the range has been from 15 to 20 per cent of a slightly subnormal count at this early period. Following this lymphopenia, there is ordinarily a rapid rise in percentage and total number to a peak toward the end of the first week, with a gradual return toward normal. It is to be noted that the large lymphoid elements form a considerable percentage of the count. In one case they formed 20.5 per cent of a 8,800 count; in another, 20 per cent of a 6,800 cell count; and in general, from 10 to 15 per cent at the peak of their appearance in the blood stream.

The monocyte reaction varies. In general, as in this case, there has been a tendency to an increased percentage during the early leukopenic

TABLE 4.—*Blood Cell Count in a Case of Measles*

		Neutrophils		Eosinophils		Basophils		Small Lymphocytes		Large Lymphocytes		Large Mononuclears		Transitionals	
1924	Total	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
5/24	4,800	70.5	3,381	3.5	168	0.0	00	16	768	5.5	264	0.0	00	4.5	216
5/25	5,000	65.5	3,275	8	400	0.5	25	15	750	6	300	0.5	25	4.5	225
5/26	5,400	44	2,376	5	270	0.0	00	29	1,566	11.5	621	2	108	8.5	459
5/27	5,400	34	1,836	5	270	0.0	00	44.5	2,403	9.5	513	1	54	6	324
5/28	6,400	47	3,008	6	384	0.0	00	34.5	2,208	6	384	0.0	00	6.5	416
5/29	6,200	57	3,534	3.5	217	0.0	00	27	1,674	7	434	0.0	00	5.5	341
5/30	8,600	64	5,504	3	258	0.5	43	22	1,892	1	86	0.0	..	9.5	817
5/31	8,400	58.5	4,914	1.5	126	0.5	42	28.5	1,394	2.5	210	0.0	00	8.5	714
6/ 1	6,200	65	4,030	5.5	341	1	62	18	1,116	3	186	0.0	00	7.5	465
6/ 2	9,800	61.5	6,027	3	294	0.5	49	24.5	2,401	4.5	441	0.0	00	6.5	637
6/ 3	5,800	60.5	3,509	3.5	203	0.0	00	25.5	1,479	5	290	0.0	00	5.5	319
6/ 4	8,800	59.5	5,236	3	264	2	176	22.5	1,980	4.5	396	0.5	44	8	704
6/ 5*	10,400	68.5	7,124	2	208	0.5	52	22.5	2,340	2	208	0.0	00	4.5	468
6/ 6	8,000	61.5	4,920	0.0	00	0.0	00	27.5	2,200	4.5	360	0.0	00	6.5	520

* Afternoon count.

Clinical Data: There was a history of onset on May 23, with symptoms of a cold with "running nose" and watery eyes. The rash appeared on the evening of the same day. On admission, there was a discrete, blotchy, macular eruption over the face, neck and upper part of the chest. The temperature rose to 102 F. On May 25, albumin, leukocytes and hyaline casts were found in the urine. On May 26, the patient was afebrile. On May 27, the temperature was 90 F.; subsequently, he was afebrile. There was no continued nephritis.

stage, rising in some cases to from 15 to 20 per cent. Less commonly there has been a reduction in percentage and total number, the lowest having been 3 per cent of a total count of 2,600 cells. In the later period of the disease there has generally been a moderate and irregular rise in percentage and total number.

Generally for two or three days following the height of the rash, cells described under smallpox as capillary endothelial cells are found in the blood smears, in small percentage. In this case they are included in the large mononuclear percentage.

Interpretation.—We believe that in measles the reduction in the number of neutrophils is due to an inhibition either of marrow production or of marrow output of these cells comparable to the condition existing in influenza and typhoid fever. We are further convinced that

the extreme reduction of neutrophils in the circulating blood lowers the defensive mechanism of the body and is largely responsible for the occurrence of pyogenic complications in measles and influenza.

The lesions in the skin and mucous membranes appear to be responsible for the stimulation of the eosinophils to hyperplasia.

The lymphocytes in their curve and in the large percentage of large forms show the action of a toxin on lymphoid tissue. There is depression in number, recovery and excess reaction. We are personally inclined to see in this reaction the response to the infection which results in immunity.

The monocyte group shows an irregular increase which may possibly be explained by the part they play in the cellular exudate in the skin

TABLE 5.—*Blood Cell Count in a Case of Mumps*

		Neutrophils		Eosinophils		Basophils		Small Lymphocytes		Large Lymphocytes		Large Mononuclears		Transitionals	
1925	Total	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
5/ 5	9,150	76.2	6,972	0.4	37	0.4	37	9	823	4.8	439	0.2	18	9	823
5/ 6	6,450	67	4,321	0.0	00	0.5	32	14	903	3.5	226	3	19	12	774
5/ 7	4,900	52	2,548	1.5	73	0.5	25	26	1,274	7	343	0.0	..	13	777
5/ 8	5,100	49	2,499	7	357	0.5	26	26	1,326	4	204	0.0	..	13.5	688
5/ 9	6,000	37.5	2,250	9.5	570	0.0	00	33.5	2,010	5.5	330	0.5	30	13.5	810
5/10	11,800	36.5	4,307	6	708	0.0	00	46	5,428	8	944	0.0	00	3	354
5/11	8,350	33	2,755	4.5	375	0.5	41	49	4,091	10	835	1	83	2	167
5/12	.....	.....	.....	...	...	...	..	..	.....	...	...	...	..	...	...
5/13	15,050	42.5	4,606	4.5	497	0.0	00	45.5	5,027	6.5	718	0.0	00	1	110
5/14	12,750	47	6,392	2.5	319	0.0	00	39	4,972	8.5	883	0.0	00	3	382
5/15	11,700	55	6,235	2.5	293	0.0	00	33.5	3,919	5	585	0.0	00	3.5	410
5/16	13,850	57.5	7,964	4.5	623	0.0	00	31	4,293	3.5	485	0.0	00	3.5	485
5/17	15,050	49	7,374	4.5	677	0.5	75	36	5,418	3.5	526	0.0	00	6.5	978
5/18	16,000	56	8,960	3.5	560	1.0	160	33	5,280	2	320	0.0	00	4.5	720

Clinical Data: The patient was exposed to mumps three weeks before admission. She had pain and tenderness behind the angle of the left jaw on May 4, but no swelling was noted. The orifice of the left parotid duct was reddened. On May 5, on admission, there was some swelling of the left parotid, also pain on the right side, but no definite swelling. The temperature, May 5, varied from 100.4 to 101 F. The patient was afebrile on May 8.

lesions (Mallory and Medlar). We are inclined to attribute the appearance of endothelial cells in the smears to the proliferation in the endothelium of the skin capillaries described by the same authors.

MUMPS

Summary.—There is with onset of swelling in the glands the development of a moderate leukopenia followed by a gradual return to normal and thence a moderate leukocytosis.

There is early a percentage increase in neutrophils, followed by a gradual decrease in percentage and in total number. In one case, on the sixth day the neutrophils were but 21 per cent of a 6,650 count. There was gradual recovery and a late neutrophil leukocytosis.

After an early deficiency, one finds an increase in percentage and total number of eosinophils in reactive individuals.

After an early depression the lymphocytes show a marked reaction with a decided lymphocytosis which precedes the neutrophil leukocytosis. The percentage maximum in the cases counted was 72 per cent.

The monocytes after an early increase in percentage and total number fall in both to show a late recovery in the case reported. In other cases the total number as well as the percentage has still been low at the end of the second week.

Interpretation.—We are inclined to interpret these changes, as in the previous diseases, as indicating a primary attack on the infecting agent by the neutrophil leukocytes, and a subsequent response on the part of the lymphoid tissue to toxins produced during the disease.

GENERAL SUMMARY

While there is considerable diversity shown by the leukocyte pictures presented in the foregoing, there appears to us to be a general similarity of plan of reaction in these diseases, especially of the neutrophil and lymphocyte cells. The apparent diversity of picture depends on exaggeration of various features of this plan. There seems to be an early reaction of the neutrophil leukocytes in all these diseases. This is most pronounced and most prolonged in scarlet fever. This is followed by a depression in number of these cells and even by an inhibition of their production or supply, most marked in measles. This depression is followed by a return to normal and to a moderate leukocytosis, most evident in smallpox, in which the local skin lesions apparently are responsible. The lymphoid cells, on the other hand, show an early depression in number, followed in every case by a definite curve of reaction, with lymphocytosis often of marked degree at the peak. We believe that in the case of the first cell, the neutrophil, we have the reaction to living organisms and the local injury produced by them, and in the case of the second cell, the lymphoid group, the reaction to toxins.

The eosinophil reactions appear to be connected with inflammations in the skin and mucous membrane, although it is to be noted that emigrated eosinophils are constantly found in lymphoid tissue when it is subject to toxic injury.

The monocyte reactions have not been sufficiently uniform to give evidence of a general type of reaction.

These pictures are not presented as being of value in the diagnosis and differentiation of the infectious diseases, yet they have been used practically in conjunction with suggestive clinical evidence in leading to the isolation of patients before the distinctive manifestations of the particular infection have appeared.

EFFECT OF MERCUROCHROME-220 SOLUBLE ON THE GERMICIDAL PROPERTIES OF FRESH DEFIBRINATED BLOOD*

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During the last few years several germicidal dyestuffs intended for intravenous injection have been introduced into therapeutics, the most notable examples of which are acriflavine, gentian violet, acriviolet and mercurochrome-220 soluble. These substances are relatively nontoxic to the animal organism as a whole, and comparately large amounts can be injected with few apparent ill effects. Clinical reports following the use of these chemicals in septicemia and related conditions have on the whole been encouraging, although, due to the difficulty of estimating the value of any therapeutic procedure in conditions with such varying courses as the septicemias, it is felt that the problem should be approached from as many angles as possible.

The ideal method of investigating a drug intended for use in human infections is the treating of animals infected with the same organism against which the drug is to be used. This has been done by Meleney and Zau [1] in the case of acriflavine, and it is possible that the method used by them would also yield important information concerning the other substances.

Normal blood, however, possesses bactericidal and bacteriostatic properties that can easily be estimated by experiments in vitro, and an attempt has been made to determine the effect of the addition of mercurochrome in varying concentrations on these properties. The experimental work leading to the introduction of mercurochrome together with clinical results has recently been collected into one review by Young, Hill and Scott.[2]

TECHNIC

Three cubic centimeters of freshly drawn defibrinated human blood were placed in each of nine test tubes. One-tenth cubic centimeter of a solution of mercurochrome of such strength as to give the desired concentration in the total

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*From the Laboratory Service, Army and Navy General Hospital, Hot Springs, Ark.

1. Meleney, F. L., and Zau, Z. D.: Action of Acriflavine on Blood and Certain Tissues of Rabbits, J. A. M. A. **84**:337 (Jan. 31) 1925.

2. Young, H. H.; Hill, J. H., and Scott, W. W.: Treatment of Infections Diseases with Mercurchrome-220 Soluble, Arch. Surg. **10**:813 (May) 1925

volume was then added to each tube, except the ninth, which received 0.1 c.c. of salt solution and served as a control. After mixing, 0.1 c.c. of a bacterial suspension was added to each tube, about four minutes elapsing between the addition of the mercurochrome and the bacteria. A tenth tube, containing 3 c.c. of salt solution, also received the same amount of bacterial suspension. This last tube was plated out immediately in order to determine the number of organisms present at the beginning of the experiment.

B. coli, Staphylococcus aureus and *Streptococcus hemolyticus* were used as test organisms. The bacterial suspensions were twenty-four hour broth cultures, undiluted in the case of the colon bacillus, diluted 1:10 for the streptococcus, and to 1:100 for the staphylococcus. Preliminary tests showed that these dilutions were advisable in the case of the streptococcus and staphylococcus in order to prevent overwhelming growth and the masking of any differences in the tubes. After inoculation, the tubes were placed in the incubator at 37 C. Dilutions were made and plates poured at the end of two hours for the colon bacillus, and after twenty-four hours for the staphylococcus and streptococcus. One-half cubic centimeter of defibrinated blood was added to the plates in the case of the streptococcus. The colonies developing were counted after forty-eight hours' incubation.

Mode of Action of Normal Blood.—The bactericidal action of blood against *B. coli* seems to reside entirely in the plasma and to be dependent on the presence of complement. Fresh serum possesses the property to a greater degree than does defibrinated blood, and both serum and defibrinated blood are rendered inert by being heated to 56 C. for one-half hour. Serum kept in the icebox remains active for several days, but shows gradual deterioration. Also, when a heavy suspension of *B. coli* is added to serum there is a distinct clearing of the tube after being kept at 37 C. for two hours, showing that the killing of the bacteria is accompanied by lysis.

When staphylococci are added to defibrinated blood, active phagocytosis of the organisms takes place, and can be seen on smear preparations. This phagocytosis apparently does not destroy any great number of the organisms, although it markedly retards their development, since staphylococci grow luxuriantly in fresh serum. Profuse growth also takes place in defibrinated blood heated to 56 C. for one-half hour or kept over night in the icebox, this effect apparently being brought about in both instances by injury to the leukocytes.

The use of *B. coli,* therefore, tests the effect of any foreign substance added to the blood on the complement and amboceptor contained in the serum, while *Staphylococcus aureus* shows any deleterious action of the added substance on the leukocytes. It is of course possible that other factors are involved. I made no observations as to the cause of the restraining effect of blood on streptococci, although this is probably also to be attributed to the cellular elements rather than to the serum.

The experimental results, which are surprising when found in a germicide used for intravenous medication, are shown in table 1. The dilution of mercurochrome in the blood stream following a therapeutic dose is about 1:13,000 to 1:15,000. These concentrations do not interfere with the disposal of *B. coli,* and the difference between untreated blood (tube 9) and blood containing mercurochrome 1:400 (tube 2) is probably within the limits of error of the experiment. When

mercurochrome is present, however, in the concentration of 1 : 200, the bactericidal power of the blood is entirely destroyed.

Staphylococci and streptococci grow better in blood containing even 1 : 25,600 mercurochrome than in normal blood. As the concentration of mercurochrome increases, the growth becomes in general more profuse, reaching a maximum at 1 : 400 for the staphylococcus and at 1 : 800 for the streptococcus. If the mechanism of interference with the normal bacteriostatic power of blood was not understood, mercurochrome would seem an enrichment material for bacterial growth when added to fresh blood, somewhat like the addition of glucose to broth.

Tubes containing mercurochrome 1 : 100 were not included in these protocols, since it was found that this concentration coagulated the serum after incubation over night. Preliminary tests showed, however,

TABLE 1.—*Bacteria Per Cubic Centimeter in Defibrinated Blood Containing Varying Proportions of Mercurochrome*

	Dilution of Mercurochrome	Bacillus coli †	Staphylococcus aureus ‡	Streptococcus hemolyticus ‡
1	1:200	600,000	1,010,000	0
2	1:400	550	22,100,000	220,000
3	1:800	200	9,600,000	1,100,000
4	1:1,600	460	10,400,000	380,000
5	1:3,200	310	9,200,000	180,000
6	1:6,400	370	10,800,000	440,000
7	1:12,800	290	8,100,000	410,000
8	1:25,600	390	4,100,000	480,000
9	Control blood alone	250	500,000	16,000
10	Salt solution*	420,000	3,300	4,100

* Tube 10 was plated immediately after inoculation with bacteria, and the figures therefore show the number of bacteria per cubic centimeter at the beginning of the experiment.
† Plated 2 hours after the addition of mercurochrome and bacteria to the blood.
‡ Plated after 24 hours.
Tubes 1 to 4 showed marked hemolysis after incubation for twenty-four hours.

that this concentration after twenty-four hours' incubation sterilizes the blood for staphylococci as 1 : 200 does for streptococci.

These experiments show, then, that mercurochrome not only interferes with the normal antibacterial properties of blood, but also that staphylococci and streptococci grow well in defibrinated blood containing mercurochrome in the concentration of 1 : 25,600 to 1 : 400. The bactericidal power of mercurochrome is destroyed by blood. A somewhat similar observation has been made in regard to hemolysis. Mercurochrome is hemolytic when added to washed red blood cells suspended in salt solution. The experiment shown in table 2 was carried out by adding 0.1 c.c. of a 50 per cent. suspension of washed human red blood cells to 1 c.c. of successive dilutions of mercurochrome in human serum and in salt solution, and recording the results after two hours at 37 C. It is obvious that the presence of serum exerts a marked protective action on the blood cells. Mercurochrome is both bactericidal and hemolytic, although it has a much greater affinity for the colloidal micellae

of blood plasma than it has for red blood cells or bacteria. This protective action of serum probably explains why mercurochrome can be given in relatively large doses without causing hemolysis, and the same action would seem to prevent any bactericidal effect. In the tubes of defibrinated blood incubated for twenty-four hours (table 1) there was always marked hemolysis in tubes 1 to 4. Since active multiplication of staphylococci and streptococci had taken place in these tubes, this fact would seem to indicate that, even in the presence of serum, mercurochrome is much more toxic for red blood cells than it is for bacteria.

It may be pointed out here that Bloomfield [3] has reported a significant experiment in which mercurochrome failed to exert any marked bactericidal effect in vitro. An area of the tongue was painted with a 10 per cent. solution of mercurochrome, especial precautions being taken to prevent contamination from adjoining areas. Culture of the painted

TABLE 2.—*Hemolytic Action of Mercurochrome in Salt Solution and in Serum for Two Hours at 37 C.*

Concentration of Mercurochrome	Serum	Salt
1:100	++	++
1:200	+	++
1:400	0	++
1:800	0	++
1:1,600	0	++
1:3,200	0	++
1:6,400	0	++
1:12,800	0	++
1:25,600	0	+
1:51,200	0	±
1:102,400	0	0
Control	0	0

++ indicates complete hemolysis and 0 no hemolysis.

area ten minutes later showed profuse growth of green streptococci, though the dye had penetrated to such an extent that the area remained discolored for twenty-four hours.

I have been unable to correlate the experiments here reported with some of those in the literature, notably of Hill,[4] showing a bacteriostatic action of the blood following the injection of mercurochrome, and have, of course, been absolutely unable to confirm the observation of Piper [5] that streptococci were killed by a dilution of mercurochrome of 1 : 8,000 in defibrinated blood.

Young, Hill and Scott [2] state that it is probable that the direct action of the drug on the bacteria in the blood stream or in local lesions is only one of the many factors involved. As a result of the work here reported, I believe that the question of a direct action of mercurochrome on bacteria in the blood stream can be definitely eliminated.

3. Bloomfield: Bull. Johns Hopkins Hosp. **34**:65, 1923.
4. Hill: Bull. Johns Hopkins Hosp. **34**:372, 1923.
5. Piper: Am. Jour. Obst. & Gynec. **4**:235, 1922.

Also, the possibility of damage through injury to the normal antibacterial properties of blood may be more than theoretical and may constitute a real source of danger from the drug. The use of mercurochrome in septicemia thus seems to be purely empiric, and the determination of its efficacy must rest entirely on the judgment of clinical experience. There should be a general appreciation of the fact that there are marked defects in the theoretical basis for its use, although it can in no way be urged as a result of this work that the drug should be abandoned. The problems of chemotherapy are intricate. Quinine is known to have an injurious effect on leukocytes,[6] although this fact in no way interferes with its efficacy in malaria. Also, as noted in a recent review by Voegtlin,[7] arsphenamine in the concentration of 1:1,000 has no effect on the motility or viability of *Spirochaeta pallida,* although this concentration is many times stronger than that attained in the tissues after a therapeutic dose.

SUMMARY

Mercurochrome in the concentration of 1:25,600 to 1:400 has no appreciable effect on the bactericidal activity of fresh defibrinated blood toward the colon bacillus; 1:200 mercurochrome completely destroys this activity.

Staphylococci and streptococci grow much more luxuriantly in blood containing 1:25,600 to 1:400 mercurochrome than they do in fresh defibrinated blood without mercurochrome. This effect seems to be brought about by an injurious action of mercurochrome on the leukocytes, and constitutes at least a theoretical objection to its use intravenously.

Any beneficial results following the clinical use of mercurochrome in septicemia cannot be attributed to a specific action of mercurochrome on the causative micro-organism. Its use in septicemia is entirely empirical. If clinical reports concerning the use of mercurochrome continue to be favorable, the manner in which it exerts this effect remains a problem yet to be worked out.

6. Fleming: Brit. M. J., 1924, p. 1114.
7. Voegtlin: Physiol. Rev. **5**:63, 1925.

THE EFFECT OF SOLUTIONS OF COPPER SULPHATE ON DUCKS*

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Since August, 1924, in addition to other lines of inquiry, some experiments with solutions of copper sulphate and their effects on ducks have been undertaken. The purpose of this work was to ascertain whether or not such solutions would have any anthelmintic value, particularly in the case of the trematode, *Echinostoma revolutum,* infesting the intestines of such wild water fowls as the scaup duck (*Marila*), etc., found on local ponds. This worm is capable of infecting a variety of water fowls, and has been established successfully in domestic ducks by Johnson [1] in an experimental way.

Chandler [2] has reported some interesting experiments with solutions of various copper salts in varying dilutions and their effects on the snail hosts of larval trematodes. This work was carried out with eight different species (six genera) of snails. Chandler's work showed that all these species of snails died after exposure for forty-eight hours to a 1 : 500,000 to 1 : 1,000,000 dilution of copper sulphate. Some died in a similar period of time in 1 : 1,500,000 to 1 : 2,000,000 dilutions. A 1 : 2,500,000 to 1 : 5,000,000 dilution killed 50 per cent in forty-eight hours, while in a 1 : 10,000,000 dilution all snails revived after being returned to untreated water. Snail eggs in intact jelly masses were not killed by fourteen days' treatment, although the embryos developed more slowly than the controls. Copper sulphate compared favorably with other copper salts in toxicity, but, on account of its cheapness, of itself would be a more desirable agent to use for antimollusc treatment of ponds and streams.

So far as can be ascertained, no work has been done that would show the effect of such treatment as the foregoing on the larval trematodes and cysts harbored by such snails so treated, or its effect on *Miracidia*. However, it is well known that cysts are resistant to many types of severe treatment. No doubt the trematodes, with the possible exception of the cysts, are quickly killed.

It would seem that such a method of control as Chandler advocates would be lessened in value on account of the resistance of snail eggs.

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1. Johnson, John C.: The Life Cycle of Echinostoma Revolutum (Froelich), Univ. Calif. Pub. Zool. **19**:335-388, 1919.

2. Chandler, A. C.: Control of Fluke Diseases by Destruction of the Intermediate Host, J. Agric. Res. **20**:193-208, 1920.

This, however, and the possible resistance of cysts, it seems, are immaterial; a properly timed serial application of sufficient copper sulphate would succeed in eliminating all molluscan hosts.

These results of Chandler led to the investigation of the effect of copper sulphate on adult worms in the intestines of ducks, and whether or not this salt would prove of any value for such use in dilutions as high as that efficacious against snails. If such should prove to be the case, we should have the curious example, in the case of water fowls at least, of a trematode being attacked at both phases of its life cycle at the same time by the same agent: on the one hand, destruction of its intermediate host, and on the other hand, destruction of its own adult form.

Up to the present time, no results have been obtained that would settle the question of the anthelmintic value of copper sulphate in ducks. This was due to the lack of infected material. It is hoped that future experiments will clear this up. However, several interesting facts were found which conform closely with the results reported by Mallory [3] dealing with the feeding of copper to laboratory animals as incidental to a study of hemochromatosis in man. It is my purpose in this paper to set forth the effects of copper sulphate on ducks without reference to any value it may have as an anthelmintic agent.

METHODS OF STUDY

Three varieties of ducks were used for these experiments. In the first experiment, a mallard and a muscovy; in the second, white pekins were used. Copper sulphate was administered in the water supplied to them. This was begun at a 1 : 1,000,000 dilution and increased at varying intervals until a 1 : 2,000 dilution was reached.

Owing to limitations of time, only the livers were sectioned and studied. These were fixed in the ordinary fixing agents, such as Bouin's fluid, Zenker's fluid, formaldehyde, etc. Sections were cut 7½ microns and stained in various ways. A variety of both acid and basic dyes were used to bring out the characteristics of the granules as stated by Mallory.[3]

Sections were made from the livers of normal ducks that received no copper at any time. These served as controls against those that received the varying dilutions. Material from the controls and from the treated ducks was subjected to an identical technic, so that a truly comparative picture was obtained.

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3. Mallory, F. B.: The Relation of Chronic Poisoning with Copper to Hemochromatosis, Am. J. Path. **1**:117-133, 1925.

RESULTS OF EXPERIMENTS

In all, fourteen ducks were used in these experiments; they were divided into two groups. The first group included two birds, a mallard male and a muscovy female. These were subjected to simultaneous treatment with the copper solutions. The remaining twelve ducks were white pekins and constituted another experimental group. Even though such a small number of birds was used, clear-cut results were obtained.

The first group of two birds was carried entirely through the treatment to necropsy before the second group was started; this was intended to serve as a preliminary experiment to determine the degree of tolerance which might be shown toward copper sulphate solutions before attempting to find its anthelmintic action. At necropsy of these two ducks the question of anthelminthiasis was temporarily abandoned, and the next group of ducks was used to check up the findings.

Table 1 gives in brief the entire history of the first group.

In the case of the muscovy, at necropsy the liver was found to be abnormally large, friable and heavily loaded with fat. The abdominal fat deposits, although not excessive in amount, presented an abnormally deep yellow coloration. The contents of the gizzard and intestine responded to tests for copper, although not so strongly as was expected. This fact appears to indicate that the copper was slowly removed from the intestine by absorption, or that it was transferred to an insoluble form. Subsequent tests appeared to indicate that both these things happen. Although no attempts were made to carry out elaborate quantitative tests, the liver tissues gave an unmistakable response to the ferrocyanid test for copper when macerated with a small quantity of distilled water and the resulting solution filtered, decolorized and concentrated by evaporation. It seems that some of the copper taken into the alimentary tract may leave in an insoluble form. This was indicated when a sample of the intestinal solution was digested with nitric acid and tested in the same way as the untreated samples of the same kind. In this case, the reaction, although small, was unmistakably more pronounced than in the case of the other samples from the same source. Both tests were made with like volumes and read in tubes of uniform bore against an opalescent background. This finding, however, was not confirmed in another test performed subsequently.

No sections were made from the liver of this duck. It was not until necropsy was performed on the mallard that it was decided to change the course of the experiments. The mallard presented a different picture. The liver of this bird was somewhat smaller than normal, and when cut, of an unnatural orange color. It was firm in texture and evidently had had a case of atrophic pigment cirrhosis. The abdominal

fat as in the case of the muscovy was abnormally yellow. On sectioning the liver and staining, granules that gave the typical reactions characteristic for hemofuscin were found in abundance.

Both these birds received identical treatment from Aug. 1, 1924, to Feb. 8, 1925, when necropsy was performed on the muscovy. On this date, the mallard was put back on a 1:10,000 dilution, on which it remained for nineteen days before necropsy. It is inconceivable that the latter fact should account for the difference in the appearance of the two livers. The liver of the muscovy resembled that seen in acute

TABLE 1.—*First Group of Ducks on Which Experiments Were Made*

Duck	Dilution of Copper Sulphate	Date Started	Age of Duck, Days	Time on This Dilution, Days	Remarks
1 (muscovy)..... 2 (mallard)	1:1,000,000 (1 mg. per liter)	Aug. 1	42	7	Both ducks same age; normal in appearance and activity
1 and 2.....	1:500,000 (2 mg. per liter)	Aug. 8	49	10	
1 and 2.....	1:250,000 (4 mg. per liter)	Aug. 18	59	10	Ducks showed desire for much water; thriving, very active, growing
1 and 2.....	1:100,000 (10 mg. per liter)	Aug. 28	69	10	No noticeable effect; healthy
1 and 2.....	1:75,000 (13.3 mg. per liter)	Sept. 7	79	10	Healthy
1 and 2.....	1:50,000 (20 mg. per liter)	Sept. 17	89	10	Healthy
1 and 2.....	1:40,000 (25 mg. per liter)	Sept. 27	99	10	Healthy
1 and 2.....	1:30,000 (33.3 mg. per liter)	Oct. 7	109	10	Healthy
1 and 2.....	1:20,000 (50 mg. per liter)	Oct. 17	119	10	Healthy
1 and 2.....	1:15,000 (66.6 mg. per liter)	Oct. 27	129	10	Healthy
1 and 2.....	1:10,000 (100 mg. per liter)	Nov. 6	139	10	Healthy
1 and 2.....	1:5,000 (200 mg. per liter)	Nov. 16	149	75	Ducks healthy, but feet and legs unnatural pallor
1 and 2.....	1:2,500 (400 mg. per liter)	Feb. 1	214	7	Muscovy sick, feathers ruffed, indifferent to food; mallard sleek but not eating well
1.....	.....	Feb. 8	221	..	Necropsy on muscovy
2.....	1:10,000	Feb. 8	221	19	Dilution increased; duck apparently healthy
2.....	.....	Feb. 27	240	..	Necropsy on mallard

phosphorus poisoning in rabbits; that of the mallard, a typical cirrhosis. Perhaps these results might be an expression of individual susceptibility; sex difference or some unknown uncontrolled condition may have been responsible.

In the second experiment, twelve white pekin ducklings were used in an attempt to analyze the effects of copper sulphate in a more careful way. The general method followed was the same as in the previous experiment, except that each individual received different treatment.

Considerable difficulty was experienced with this group of ducklings due to the fact that they early showed a tendency to rickets at least

partly due to the circumstance of being confined in an animal loft and receiving little direct ultraviolet radiation. This disease was at least a contributory factor to the death of eleven of the twelve. However, the validity of the subsequent microscopic findings with regard to the effect of copper poisoning was not influenced by this condition.

Table 2 sets forth the treatment of group 2.

Of the ducklings referred to in table 2, five were discarded. These

TABLE 2.—*Treatment of Group 2*

Dilutions of Copper Sulphate	Date Each Dilution Was Started	Age of Ducklings in Days	Ducklings Receiving Solutions*	Time of Death and Total Time in Days on Copper Solutions		
				Duckling	Date	Total Time on Solutions
0	April 17 (1925)	14	1, 2, 3, 4	1 2 3 4	May 12 May 13 May 1 June 10	Controls. Received no copper solutions
1:1,000,000 (1 mg. per liter)	April 17	14	5, 6, 7, 8, 9, 10, 11	11	April 20	3
1:500,000 (2 mg. per liter)	April 24	21	5, 6, 7, 8, 9, 10	6 10	April 29 April 29	12 12
1:250,000 (4 mg. per liter)	May 1	28	7, 8, 9	5	June 8	52
1:100,000 (10 mg. per liter)	May 8	35	7, 8, 9	..	.....	..
1:75,000 (13.3 mg. per liter)	May 15	42	7, 8, 9	..	.....	..
1:50,000 (20 mg. per liter)	May 20	47	7, 8, 9	7	May 20	33
1:40,000 (25 mg. per liter)	May 22	49	8, 9	..	.....	..
1:30,000 (33.3 mg. per liter)	May 26	53	8, 9	..	.....	..
1:20,000 (50 mg. per liter)	May 28	55	8, 9	..	.....	..
1:15,000 (66.6 mg. per liter)	June 1	59	8, 9	..	.....	..
1:10,000 (100 mg. per liter	June 4	62	8, 9	..	.....	..
1:5,000 (200 mg. per liter)	June 6	64	9	8	June 4	48
1:4,000 (250 mg. per liter)	June 8	66	9	..	.....	..
1:3,000 (333.3 mg. per liter)	June 10	68	9	..	.....	..
1:2,000 (500 mg. per liter)	June 12	70	9	9	June 15	50

* Duckling 12 died before experiment began.

were nos. 3, 6, 10, 11 and 12. In the control group were left three ducklings: no. 1 that received no copper and lived for 25 days after copper was started with the other ducklings; no. 2 that lived 26 days; and no. 4 that lived 54 days, or all but five days of the entire duration of the experiment.

It was intended that nos. 5 and 6 should be carried to the 1: 500,000 dilution and held on this until the end of the experiment. No. 5 lived to within seven days of the end, but no. 6 died too early to be used.

Nos. 7, 8, and 9 were carried to 1:50,000, 1:10,000, and 1:2,000 dilutions, respectively.

Of this group, then, were seven ducklings that may be analyzed as in table 3, in which the figures following the dilutions indicate the time the ducklings were held on each dilution of copper sulphate.

The comparative time-dilution coefficients were obtained from the formula $\frac{3.9}{AD/T}$ in which AD is the average dose, T the total days lived, and 3.9 the AD/T of duckling 9 expressed as 3.9 thousands. The coefficients, then, are in terms of duckling 9. These coefficients were obtained in order to find whether or not the observed microscopic effects of copper sulphate were a function of two variables or of one variable. In other words, would a high dilution for a long time give the same

TABLE 3.—*Analysis of Seven Ducklings Chosen from table 2*

Dilution of Copper	Duck No.						
	1	2	4	5	7	8	9
1:1,000,000	0	0	0	7	7	7	7
1:500,000	0	0	0	45	7	7	7
1:250,000	0	0	0	..	7	7	7
1:100,000	0	0	0	..	7	7	7
1:75,000	..	..	0	..	5	5	5
1:50,000	..	..	0	..	..	2	2
1:40,000	..	..	0	..	..	4	4
1:30,000	..	..	0	..	..	2	2
1:20,000	..	..	0	..	..	4	4
1:15,000	..	..	0	..	..	3	3
1:10,000	..	..	0	..	..	..	2
1:5,000	..	..	0	..	..	..	2
1:4,000	..	..	0	..	..	..	2
1:3,000	..	..	..	..	..	..	2
1:2,000	..	..	..	..	..	..	3
Total days lived...	25	26	54	52	33	48	59
Average dose of copper sulphate	None	None	None	1:567,307 for 52 days	1:388,636 for 33 days	1:286,967 for 48 days	1:234,237 for 59 days
Comparative time-dilution coefficient	0	0	0	0.358	0.333	0.661	1.000

effect as a low dilution for a short time; or, is the strength of the solution more effective than the time, or vice-versa?

It is admitted that the number of cases in this experiment is far too small to settle any such question as this. However, a lead is furnished in the cases of ducklings 5 and 7. The coefficient of duckling 5 is somewhat higher than that of 7. The effects found in the case of duckling 7 were greater than in duckling 5, indicating that strength of solution is the most important factor in producing the effects of copper poisoning. This, in fact, might be naturally expected.

Numerous sections were prepared from the livers of all these ducklings. In no case were any granules of pigment that could be interpreted to be hemofuscin found in the controls. Duckling 5, which received the least copper sulphate (2 mg. per liter for forty-five days), showed a small but entirely characteristic pigmentation in the liver with

granules that behaved in every way like hemofuscin. The amount of pigmentation found in duckling 7 was considerably greater than in the case of duckling 5; in duckling 8 greater than in duckling 7; and in duckling 9 an extensive pigmentation was encountered in the liver cells, endothelium and connective tissue of the liver. These four ducklings formed a roughly graded series of pigmentation, corresponding in a general way to the dosage of copper.

In no case were granules found that could be considered to be hemosiderin. Hemofuscin is transformed into hemosiderin very slowly, and years are probably required for the process. According to Mallory,[3] two to three years are required before a good reaction may be obtained for hemosiderin in the rabbit; the sheep shows granules of hemosiderin in less than one year.

The livers of all the ducklings except the last one appeared normal or practically so at necropsy. That of the last one showed moderate atrophy but pronounced coloration. No noticeable external symptoms, except slight paling of the feet and legs in the case of duckling 8, that could be adjudged due to the copper, were seen in any case except that of duckling 9. The symptoms seen in the case of duckling 9 were practically the same as those noted for the muscovy in group 1. None of the individuals of group 2 showed as pronounced paling of the feet and legs as those of group 1. This was due, no doubt, to the much shorter duration of the second experiment.

COMMENT

The foregoing results indicate that copper sulphate is able to bring about in ducks the series of changes that are responsible for the production and deposition of hemofuscin. In these experiments, search for this pigment was made only in the liver. However, it may be widespread in the body as the results of other workers have shown.

Mallory, Parker and Nye,[4] as incidental to a study of the histological changes in man due to hemochromatosis, noted the pigmentation obtained in rabbits from chronic poisoning with copper acetate. Mallory [3] reported similar experiments with metallic copper powder. He also stated that zinc would produce the same pigmentation.

The exact nature of hemofuscin has not been shown. Mallory states that "it is probably only an intermediate product between hemoglobin and hemosiderin with properties different from either. It is preserved by all fixatives, is insoluble in water and dilute acids and stains deeply with basic aniline dyes while hemoglobin stains with acid dyes and hemosiderin with neither."

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4. Mallory, F. B.; Parker, Frederic, Jr.; Nye, Robert N.: Experimental Pigment Cirrhosis Due to Copper and Its Relation to Hemochromatosis, J. M. Res. **42**:461-490, 1921.

The presence of copper in hemofuscin has never been demonstrated. Copper does, however, form a compound, cuprohemol, with hemol, a reduction product of hemoglobin. According to MacCallum,[5] hemofuscin is also iron-free. The role of hemofuscin in the iron cycle, pathologic or otherwise, will be elucidated only by future studies.

The paling of the deep yellow color of the feet and legs of several of the ducks used in this study, together with the deepening of the yellow color of the abdominal fat, as noted above, may indicate that the carotinoid pigment (probably xanthophyll) responsible for this coloration may also be influenced by an overdose of copper sulphate. This color reaction was noted in both the birds of group 1 and in two of group 2. The nature of the processes involved in this case are not known, since no preparations were made except from the livers. Parker[6] called attention to the common observation of poultry men that the external yellow pigmentation of hens is paled after a prolonged egg-laying period. Studies have shown that this is not due to extraction of pigment from the external parts but to a diversion of pigment to the ovaries, where it is utilized in the egg-making process. Such studies have not definitely determined whether this pigment is a necessary factor, perhaps associated with vitamin A as has been suggested, or whether such a method of utilization as the foregoing furnishes an easier route of excretion for the fat-soluble pigment. It is certain that the pigment in the skin is paled not by resorption but by the lack of new pigment being deposited in the cells of the malpighian layer and by a process of excretion brought about by the gradual replacement of the epithelium.

It is probable that copper sulphate would present only negligible dangers if used as an anthelmintic for ducks and other fowls. Certainly, in my work, no definite external symptoms, except paling of the feet and legs, were noted until the solution supplied to the ducks contained 400 mg. of copper sulphate per liter, which is a comparatively strong solution. Since copper sulphate solutions, if they should prove of value as anthelmintic agents, would not be used as strong as 400 mg. per liter, nor for extended periods, the danger would be lessened materially. A slight production of hemofuscin in the liver and other organs, under such circumstances, would be, it seems, without any especial significance. The changes in the external carotinoid pigment would serve as a signal of danger, if such changes can be shown to be due to the copper treatment.

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5. MacCallum, W. G.: A Textbook of Pathology, ed. 2, Philadelphia: W. B. Saunders Company, 1922.

6. Parker, Leroy S.: Carotinoids and Related Pigments. The Chromolipoids, New York: The Chemical Catalog Co., 1922.

SUMMARY AND CONCLUSIONS

Copper sulphate solutions produced pigmentation in the livers of ducks. This pigment was hemofuscin.

Definite pigmentation was produced in one instance with a 1 : 500,000 (2 mg. per liter) dilution of the salt.

Further study is needed to determine the nature of the changes in the carotinoid pigments as well as the pigments derived from the hemoglobin.

Copper sulphate would not have any ill effect if it should be used for an anthelmintic in ducks, provided its concentration does not go above approximately 100 mg. per liter and if it is not used continuously.

ANEURYSM AND ANOMALY OF THE CIRCLE OF WILLIS *

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True aneurysms of the cerebral arteries are to be sharply distinguished from the so-called miliary aneurysms of the brain. The latter are said to be demonstrable by maceration methods in almost every case of cerebral apoplexy occurring after 40 (Osler).[1] They are usually about as large as a pinhead, involve the finer vessels within the brain, and frequently (Pick)[2] are simply minute hematomas representing hemorrhages which have occurred from direct rupture of the vessel wall. The former, on the other hand, are less common, having been encountered in from 0.2 to 1.5 per cent. of various series of necropsies (Pitt,[3] Osler, Reinhardt,[4] Fearnsides[5]). Three have been encountered in 1,308 necropsies performed at the Michael Reese Hospital since 1909. They may occur at almost any age, involve as a rule the large vessels at the base of the brain, occasionally those of the convexity, and are usually the size of a pea or a cherry pit, becoming in some instances as large as a walnut or even a small orange.

True cerebral aneurysms are of pathologic interest chiefly because of the difficulties frequently involved in establishing their etiology. Because of these difficulties, many of the aneurysms of obscure etiology reported in the literature, particularly those occurring in persons in the earlier decades of life, have been attributed by exclusion to hypothetical congenital hypoplastic defects in the vessel walls. Attention has been called, however, to the frequency of gross developmental anomalies of the vessels at the base of the brain by the anatomic studies of Windle,[6] Parnisseti,[7] Wyrubow[8] and DeVries.[9] The possible causal relation-

* From the Otto Baer Fund for Clinical Research of the Michael Reese Hospital and the Nelson Morris Memorial Institute for Medical Research.

1. Osler, W.: The Principles and Practice of Medicine, New York, D. Appleton & Co., 1912.

2. Pick, L.: Ueber die sogenannten miliaren Aneurysmen der Hirngefässe, Berl. klin. Wchnschr. **47**:325 and 382, 1910.

3. Pitt, W.: On Cerebral Embolism and Aneurysm, Brit. M. J. **1**:827, 1890.

4. Reinhardt, A.: Ueber Hirnaneurysmen und ihre Folgen, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **26**:432, 1913.

5. Fearnsides, E. G.: Intracranial Aneurysms, Brain **39**:224, 1916.

6. Windle, B. C. A.: On the Arteries Forming the Circle of Willis, J. Anat. & Physiol. **22**:289, 1888.

7. Parnisseti, C., quoted by Rothman, M.: Ueber das Verhalten der Arteria cerebri anterior beim Affen, Anthropoiden und Menschen, Arch. f. Psychiat. **38**: 285, 1904.

8. Wyrubow, quoted by Rothman.

9. DeVries, B.: Sur la signification morphologique des artères cérébrales, Arch. de biol. **21**:357, 1905.

ship of such deviations to the formation of aneurysms of the basilar artery was first suggested by Lebert.[10] The point was later reiterated by von Hofmann,[11] with respect to the vessels at the base of the brain in general, with the statement: "It is not impossible that many of these anomalies can contribute to the formation of aneurysms through an uneven division of blood volume and pressure." Individual instances involving such an association have been described by Ebstein,[12] Weir Mitchell [13] and Berger.[14] More recently Busse,[15] noting the preponderance, in his experience, of aneurysms involving the anterior communicating artery, was led to make a careful anatomic study of this region. He found deviations from the normal in 227 of 400 brains examined, ranging from simple doubling of the vessel to the most intricate and fanciful plexus formation. These abnormalities were regarded by him as evidences of arrested embryologic development. In thirty-nine cases, almost 10 per cent., dilatation of some anomalous vessel in such a group had occurred, with the formation of a true aneurysm. Microscopically, the walls of such outpouchings were found to be thinned, the elastica interna stretched and sometimes broken; but no other evidences of disease or degeneration were to be made out. The possible formation of these aneurysms on the basis of purely mechanical factors was suggested, and the opinion ventured that a careful study of other portions of the circle of Willis might disclose a similar condition.

Attention is called by Merkel [16] in Henle's "Grundriss der Anatomie" to the occurrence of anomalies of the posterior communicating arteries, the vessels involved in the case to be reported. Windle, in his study of 200 brains, encountered forty-three cases in which there was a marked disparity in the size of these vessels, nine in which the right was absent, thirteen with absence of the left, and three in which both were absent. Mitchell was able to collect from the literature sixteen anomalies of the posterior communicating arteries. In nine of these, the vessels were

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10. Lebert, H.: Ueber Aneurysmen der Gehirnarterien, Berl. klin. Wchnschr. **3**:209, 229, 249, 281, 336, 345, 387, 402, 1866.

11. Von Hofmann, E. V.: Ueber Aneurysmen der Basilarterien und dessen Ruptur als Ursache des plötzlichen Todes, Wien. klin. Wchnschr. **7**:823, 1924.

12. Ebstein, W.: Aneurysma einer unpaaren Arteria cerebri anterior, Deutsch. Arch. f. klin. Med. **12**:617, 1874.

13. Mitchell, S. W.: Aneurysm of an Anomalous Artery Causing Antero-Posterior Division of the Chiasm of the Optic Nerves and Producing Bitemporal Hemianopsia, J. Nerv. & Ment. Dis. **14**:44, 1889.

14. Berger, W.: Ueber Aneurysmen der Hirnarterien, Virchows Arch. f. path. Anat. **245**:138, 1923.

15. Busse, O.: Aneurysmen und Bildungsfehler der Arteria communicans anterior, Virchows Arch. f. path. Anat. **229**:178, 1921.

16. Merkel, F.: Henle's Grundriss der Anatomie des Menchen, Braunschweig, F. Vieweg und Sohn, 1901.

absent or impervious. DeVries quotes references to forty-five anomalies of the posterior communicating arteries, in seven of which both vessels were absent. In no case in any of these series had aneurysms occurred. Indeed, except for two of the cases reported by Berger, no instances of association of aneurysms and anomalies of these vessels have been found. It is felt, therefore, that the coincidence of these conditions is of sufficient interest to justify the following report.

REPORT OF A CASE

History.—Mrs. C. T., aged 72, housewife, was first admitted to the Michael Reese Hospital, to the medical service of Dr. Solomon Strouse, on April 4, 1923. Her father died at the age of 64 "of an aneurysm." Her husband died at the age of 60 of heart trouble. She had been married for twenty-one years, but had never been pregnant. At 40 she had an attack of pleurisy. Five years later, she had had typhoid fever, and several times during the last few years some of the joints of her limbs had become stiff and swollen. Eighteen months previous to admission she had had erysipelas of the face, which subsided in about ten days. During the last two years, she had slowly lost weight and strength and was bedridden most of the time. There were occasional brief attacks of weakness and dizziness, and she had noticed that her vision was gradually becoming impaired.

Examination.—The patient was poorly nourished and restless. The blood pressure was 110 systolic and 60 diastolic. There was no cardiac enlargement. A short harsh systolic murmur was heard over the apex and was transmitted to the vessels of the neck. The pupils were round and equal, but responded sluggishly to light and during accommodation. The knee and Achilles reflexes were very active. There was no ankle clonus. The biceps and triceps reflexes were present. The Babinski sign was negative.

The following ophthalmoscopic findings were recorded: Right eye: typical retinal sclerosis with moderately tortuous vessels and punctate areas of exudate. The disk was fairly normal. Left eye: retinal sclerosis of much higher degree, with larger and more numerous areas of exudate, one of which involved the macula. Fairly advanced atrophy of the optic nerve, "probably due to the retinal atrophy."

Urine: The twenty-four hour output was 26 ounces. The specific gravity was 1.018. There was no albumin. There were occasional hyaline and granular casts.

Course of Illness.—Her course in the hospital was uneventful, except for occasional "rheumatic" muscular pains and a brief unexplained fever. She was discharged unimproved.

Second Admission.—On March 2, 1925, more than two years later, she returned. In the interval her weakness and dimness of vision had been progressive, and during the few months preceding entrance she developed a severe mental disturbance which necessitated her being confined to a sanatorium. While in a period of excitement, on the day before her final admission to the hospital she jumped from a second story window, and sustained a fracture of the left humerus. On entrance to the hospital she was completely disoriented and had hallucinations, so that restraint was required. On March 27, the temperature rose to 102 F.; evidences of consolidation appeared over both bases, and she became comatose. A

flaccid paralysis of the right arm was noted, and a final diagnosis of bronchopneumonia and possible cerebral thrombosis was made. On March 29, 1925, she died.

Necropsy.—There was bilateral pneumonia of the hypostatic type.

The heart was not enlarged. On the cusps of the aortic and mitral valves there were rows of small, firm, beadlike vegetations. The leaflets themselves were thickened and shortened as were the papillary muscles. The myocardium was of good consistency; its cut surfaces showed a moderate amount of grayish-white streaking. Microscopically, the vegetations consisted of dense fibrin and a few round cells. The valves were diffusely scarred and hyalinized and in places showed evidences of atheromatous change. About many of the small vessels in the myocardium were collections of large mononucleated and multinucleated cells with relatively large nuclei and slightly purple cytoplasm, similar to the cells described by Aschoff as characteristic of rheumatic fever.

The kidneys presented the picture of a moderately advanced chronic diffuse nephritis. Microscopically, occasional small hyaline thrombi were found in the glomeruli.

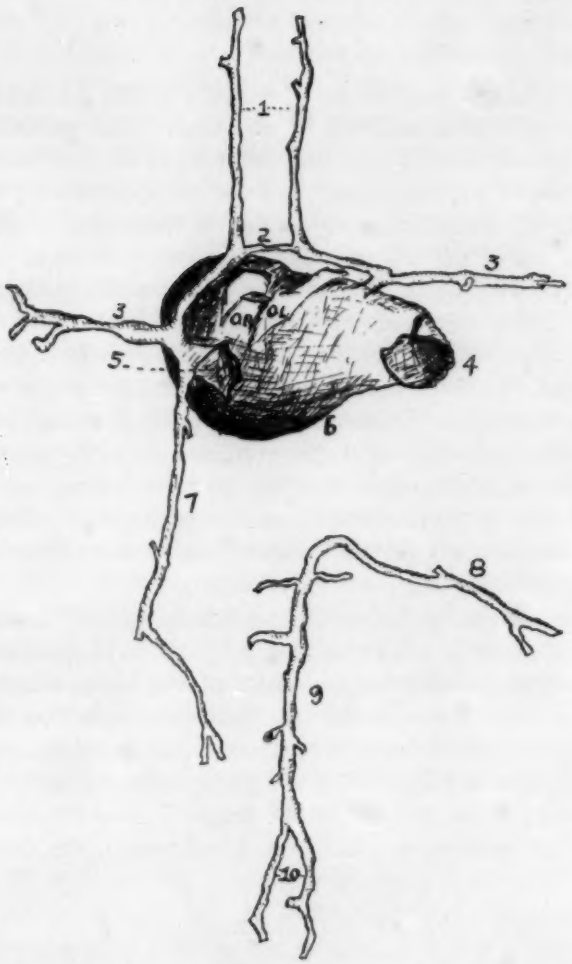
In the aorta there was an intense sclerosis of the senile type. The splenic artery was long and tortuous, with marked yellowish intimal streaking.

The findings of chief importance, however, related to the examination of the head. The pachymeninges were thickened and in places firmly adherent to the calvarium. The brain was symmetrical. The leptomeninges were diffusely thickened and whitened.

The vessels at the base of the brain were rather narrow, and in their walls were many sclerotic plaques. The vessel arising from the right internal carotid artery at the usual point of origin of the right posterior communicating artery was large and passed posteriorly between the cerebellum and the occipital lobe in the course normally taken by the posterior cerebral artery. The left posterior communicating artery was absent. The left internal carotid artery, just after its emergence from the cavernous sinus, was dilated to a diameter of 1.2 cm., and extending medially from it was a rounded aneurysmal sac measuring 2.5 by 2 by 1.5 cm. Over the superior and anterior surfaces and proceeding to the basal aspect of this sac, were spread the fibers of the optic chiasm. From the basal surface to which they had been adherent, emerged the flattened optic nerves. The left optic nerve had been reduced to a narrow compressed band. The right was less involved. The lumen of the sac was almost completely filled with a red and white thrombus. That portion of the wall of the aneurysm adjacent to the skull was composed of thin, fairly tough, white tissue. When the sac was dissected away from the brain however, its wall on this side was found to be extremely thin and blood stained; the enclosed thrombus almost protruded through it. The contiguous brain substance was also stained with blood. There was a superficial erosion of the sphenoid bone where the aneurysm had rested on it.

The vertebral arteries were about equal in size. The left posterior cerebral artery emerged from the basilar. The right posterior cerebral artery was absent.

Microscopic Examination.—Microscopically, the leptomeninges were considerably thickened and sprinkled with round cells and large mononuclear phagocytes containing iron pigment. The meningeal vessels appeared normal, and there was no infiltration of round cells about them. The posterior wall of the aneurysm was reduced to a thin layer of hyalinized fibrous tissue which was fused with the enclosed thrombus and covered by an adherent layer of compressed brain tissue in which were scattered many large cells laden with iron pigment. It was



1 indicates the anterior cerebral arteries; *2*, anterior communicating artery; *3*, middle cerebral arteries; *4*, opening of aneurysm into the left carotid artery; *5*, right internal carotid artery; *6*, aneurysm; *7*, right posterior communicating artery; *8*, right posterior cerebral artery; *9*, basilar artery; *10*, vertebral arteries; *O. R.*, right optic nerve; *O. L.*, left optic nerve.

sprinkled with many leukocytes and red blood corpuscles, and no muscle or elastic fibers could be demonstrated by the van Gieson and Verhoef stains.

A similarly stained section through the wall of the sac near its origin was composed of dense hyalinizing fibrous tissue, some young fibroblasts, and a few very fine, irregular, black elastic fibrils.

COMMENT

Berger's analysis may be applied briefly to the mechanical factors which may have been involved in this case. The pulsations of the heart are transmitted with particular intensity to the left internal carotid artery because of the direct origin of the common carotid on this side from the aorta. Particularly vulnerable to the effects of this stress is the point at which the internal carotid suddenly emerges unsupported from the cavernous sinus. Relief from this strain is normally afforded by the distribution of blood from the internal carotid into the anterior and middle cerebral and posterior communicating arteries. In the present case, however, the latter outlet was absent, and the strain was further increased by the break in the circle on the right side resulting from the abnormal course of the right posterior communicating artery. The formation of an aneurysm as a result of these factors may have been favored further by the presence of an area of lessened resistance at the site from which the left posterior communicating artery normally should have emerged.

The rôle of the extensive atherosclerosis present in the cerebral vessels in this case is not to be disregarded. It is possible that these changes were responsible for the onset of the lesion relatively late in life, while the mechanical conditions described served at best only as predisposing factors of minor importance. Busse pointed out that most of his aneurysms occurred after 40, when some degree of sclerosis is almost always present, and in both of Berger's cases the cerebral vessels were rigid and extensively calcified. Nevertheless, the relationship of atherosclerosis to the production of these aneurysms is not clear, and its importance has been minimized by Lebert, Fearnsides and Reinhardt. Certainly it is true that the most intense degree of sclerosis may confer no apparent tendency to aneurysm formation, while frequently, in cases which have been attributed by exclusion to such changes, arterial degeneration of only mild degree has been present.

Syphilis is a less frequent cause of these lesions than atherosclerosis (Kaufmann [17]) and is held responsible for a relatively small proportion of the cases in the literature. No evidences of this disease were present clinically or anatomically in the present case.

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17. Kaufmann, E.: Lehrbuch der Speziellen pathologischen Anatomie, Berlin and Leipzig, Walter De Gruyter and Co., 1922.

The cardiac lesions encountered were undoubtedly of rheumatic origin. Those aneurysms which have been attributed to mycotic embolism of the cerebral vessels have been associated with the bacterial endocarditides. However, a few cases have been recorded by von Jaksch [18] and by Löwy,[19] in which cerebral aneurysms have been accompanied by evidences of a healed or active rheumatic cardiac infection. Löwy regards such aneurysms as evidences of direct arterial damage by the infective agent, and points out that Eppinger considered angina, rheumatism and scarlet fever as important factors in the pathogenesis of these lesions. It is interesting in this connection that Pappenheimer and von Glahn [20] have described changes characteristic of rheumatic fever occurring in the aorta. The present case and those of von Jaksch and Löwy suggest the possible occurrence of similar changes involving the smaller arteries. No evidences of such involvement were found here, however, either in the aorta or in sections taken from the cerebral vessels.

Clinically there was little here on which to base a diagnosis of cerebral aneurysm. The absence of evidences of increased intracranial tension and particularly of choked disks is characteristic of these lesions (Oppenheim,[21] Beadles [22]) and may be of some diagnostic importance when accompanied by distinct focal evidences of pressure. A progressive unilateral or bilateral amaurosis as was present here is perhaps the most typical of the focal lesions produced by aneurysms in this location (Lebert). It is worthy of mention that the clinical picture may in some instances be fairly characteristic (Symonds,[23] Burchardt [24]), and that with the occurrence of one or particularly a series of apoplectiform seizures in a young person, in the presence of focal evidences of tumor, the possibility of a rupturing or ruptured cerebral aneurysm is to be considered seriously.

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18. Von Jaksch, R.: Klinische Beiträge zur Kenntnis der Gehirnaneurysmen jugendlicher Individuen, Prager med. Wchnschr. **38**:483, 1913.

19. Löwy, J.: Das Hirnarterienaneurysma als Nachkrankheit des Glenkrheumatismus, Zentralbl. f. inn. Med. **43**:505, 1922.

20. Pappenheimer, A., and von Glahn, W. C.: Lesions of the Aorta Associated with Acute Rheumatic Fever and with Chronic Cardiac Diseases of Rheumatic Origin, J. Med. Res. **44**:489, 1924.

21. Oppenheim, H.: Lehrbuch der Nervenkrankheiten, Berlin, S. Karger, 1913.

22. Beadles, C. F.: Aneurysms of the Larger Cerebral Arteries, Brain **30**: 285, 1907.

23. Symonds, C. P.: Contributions to the Clinical Study of Intracranial Aneurysms, Guy's Hosp. Rep. **73**:139, 1923.

24. Burchardt, H.: Die chirurgische Bedeutung der Gehirn-Aneurysmen, Burns Beitr. z. klin. Chir. **133**:429, 1925.

SUMMARY

In a woman, aged 73, the circle of Willis was bilaterally incomplete. The right posterior communicating artery took the course normally taken by the right posterior cerebral artery. At the site of origin of the left posterior communicating artery was an aneurysm 2.5 cm. in greatest diameter.

Cerebral aneurysm associated with anomalies of the posterior communicating arteries of the circle of Willis is rare. Abnormality in the distribution of the blood due to such anomalies may be a mechanical factor in the causation of cerebral aneurysms. The senile atherosclerosis present in the case reported may have had a part in the formation of the aneurysm, rendering the involved vessel more susceptible to the mechanical factors brought about by the anomalies of the circle of Willis.

The aortic and mitral valves and the myocardium were the seat of recent rheumatic changes. There was nothing to indicate that such changes occurring at an earlier period of life had a part in the formation of the aneurysm. There was no clinical or anatomic evidence of syphilis.

Progressive amaurosis, more marked on the left than on the right side, was the essential clinical manifestation of the condition.

CHRONIC BENZENE POISONING

REPORT OF A CASE WITH NECROPSY FINDINGS *

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Occupational poisoning with benzene enters into the experience of those of us who are removed from industrial centers so infrequently that it is prone to escape consideration in differential diagnosis in cases presenting marked hematopoietic insufficiency. Aside from its rarity, benzene poisoning is especially likely to go unrecognized because the time interval between exposure and the appearance of clinical symptoms may be several weeks, thus giving the patient time to be far removed from the site of his exposure. It is hoped that the case herein reported may be of some help in stimulating the recognition of other such cases.

REPORT OF A CASE

History.—A Norwegian laborer, aged 32, unmarried, entered the medical service of the University Hospital, May 27, 1925. He complained of bleeding from the rectum, gums, nose and into the skin, as well as soreness of the gums and weakness. He was not aware of any similar trouble ever having existed in his family. He experienced a severe attack of nosebleed at the age of 14 which lasted about an hour. He had had pneumonia during childhood and frequent attacks of bronchitis more recently. In 1918 he had bilateral otitis media complicating influenza. Except for these illnesses, he had been in good health.

On Jan. 6, 1925, the patient started to work as a "coating dough mixer" in a can factory. His work consisted in "cutting chunks of material into a large vat containing benzene." Each day on starting to work he had headache and nausea, and at times vomited. The fumes irritated his eyes, compelling him to wear goggles. Because a fellow workman who was rather pale developed a sore tongue, and because of rumors concerning the dangers of benzene, the patient left the factory, March 20, 1925, and spent the subsequent time with relatives in the country. In April, 1925, he noted both bright red and dark blood in his stools, as well as some hemorrhages into the skin. About May 10, blood blisters developed in his mouth, and on the following day the nasal secretion was streaked with blood. His gums gradually became sore and black. On May 24, his nose began to bleed profusely, and continued to bleed until his admission to the University Hospital on May 27, 1925. Two days before admission he noted showers of red spots over the legs and thighs. He had been especially weak and pale since the onset of the hemorrhage on May 24, and had fainted on his way to the hospital. He had not had chills and little if any fever.

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Physical Examination.—The patient was well developed and well nourished. He was extremely pale, but was without the yellow tinge of an hemolytic anemia. The nose was bloody, and the left nostril was packed with gauze. The lips were crusted with blood, the gums were spongy and black. The oral mucous membranes were extremely pale, with a bloody postnasal discharge, and some petechiae in the soft palate. The lymph glands were just palpable in the neck and axillae. The heart was slightly enlarged, and there was a systolic murmur along the left sternal margin. The pulse rate was 112 and and regular. The systolic blood pressure was 118, diastolic 60; temperature, 101 F. Liver dulness extended slightly below the costal margin; the spleen was not palpable. There were numerous recent petechiae and ecchymoses over the thighs and above the left clavicle. On the right thumb there was a lesion 8 by 12 mm. with a black scaly surface and a red indurated border.

The blood count revealed: erythrocytes, 860,000; leukocytes, 1,400; hemoglobin, 20 per cent. The differential count was: polymorphonuclear leukocytes, 13 per cent; lymphocytes, 48 per cent; endothelial leukocytes, 39 per cent. There was marked anisocytosis, poikilocytosis and achromia, but no macrocytes or nucleated red corpuscles were seen. The urine contained a trace of albumin. The blood Wassermann test was reported negative from two laboratories to both alcoholic and cholesterinized antigens.

Coagulation time for the venous blood was nine and one-half minutes by the Brodie-Russell-Boggs instrument and nine minutes by the capillary tube method. The capillary blood coagulated in nine minutes by each method. The fragility of the red blood cells showed a beginning hemolysis at 0.38 per cent and complete hemolysis at 0.34 per cent. Control readings were 0.42 per cent and 0.34 per cent. The blood platelets were 70,000 per cubic millimeter. Bleeding time was thirteen minutes; prothrombin time was sixteen minutes. In the retractility test, a clot was formed in thirty minutes, but was not retractile after twelve hours. The constrictor test for petechial hemorrhages was negative.

Subsequent Course.—May 27: The patient was given 250 cc. of blood by direct transfusion. This was followed in one hour by chilliness and a temperature of 103.4 F. Bleeding from the nose continued.

May 28: The maximum temperature was 103.6 F., pulse 130, respiration 24. The nasal discharge was purulent and bloody. The bladder was distended.

May 29: The maximum temperature was 104.6 F., pulse 160, respiration, 28. Epistaxis was increasing. The nose was tightly packed with gauze strips. Twenty cc. of whole blood was given intramuscularly. The urine contained neither albumin, sugar nor blood. Microscopically, there were no pus cells, red blood cells or casts.

May 30: The patient complained of pain in the left ear, and the ear drum was found to be bulging. Paracentesis allowed bloody fluid to escape, and bleeding continued for thirty minutes. One hour after receiving 550 cc. of citrated blood, the axillary temperature was 108.2 F., pulse 164, respiration 34. The patient had chills, vomited changed blood, and had a low muttering delirium.

May 31: The maximum temperature was 103.6 F., pulse 124, respiration 24. Twenty cubic centimeters of whole blood was given intramuscularly.

June 1: The maximum temperature was 104 F., pulse 128, respiration 26. The erythrocytes numbered 810,000, and there was 21 per cent of hemoglobin. Bleeding was continuous, and there was drowsiness with periods of delirium.

June 2: The maximum temperature was 104 F., pulse 136, respiration 24. The left eyelid was swollen and filled with extravasated blood.

June 3: The maximum temperature was 103.8 F., pulse 145, respiration 24. Twenty cubic centimeters of blood was given intramuscularly. The patient was irrational and incontinent. Blood culture taken May 29, 1925, was reported negative.

June 4: The maximum temperature was 103.4 F., pulse 136, respiration 26. Twenty cubic centimeters of blood was given intramuscularly. The erythrocytes numbered 860,000, and the leukocytes 4,000; the hemoglobin content was 18 per cent.

June 6: The maximum temperature was 103.8 F., pulse 140, respiration, 28. The erythrocytes numbered 720,000 and the hemoglobin content was 16 per cent. The patient attempted to get out of bed, but was not and had not been hard to restrain. He had not shown the noisy active delirium described in cases of acute benzene poisoning. There was not much change in the bleeding.

June 7: The patient died at 9:50 a. m.

Necropsy.—The body was well developed and nourished. There was little rigor mortis, no lividity and no demonstrable edema. The skin was extremely pale. There were petechial hemorrhages over the legs, above the clavicles and in both upper eyelids. The left ear was filled with a brown serous fluid. The teeth, tongue, gums and nasal mucus membranes were covered with a black blood-stained material. Smears from the gums showed both spirochetes and fusiform bacilli in small numbers. Each pleural cavity contained 125 cc. of straw colored fluid. There were many hemorrhages beneath the visceral pericardium, varying in size from that of a pin point to 3 mm. in diameter. The heart muscle was pale. The chambers contained red clot. The right lung weighed 700 Gm., the left 520 Gm. There were elevated grayish nodules a few centimeters in diameter scattered through both lower lobes and the upper lobe on the right. The remaining lung tissue was edematous. The hilus lymph nodes were slightly enlarged but soft. The spleen weighed 160 Gm. The capsule was wrinkled and the pulp was dark red. The mucosa of the stomach was hemorrhagic; there was dark blood in the lower ileum. The pancreas was normal. The liver weighed 1,960 Gm. Shining through the capsule, and on cut section, there were numerous yellowish-gray areas which were opaque and resembled necrosis more than fat. The kidneys weighed 140 Gm. and 195 Gm. right and left. They showed the light colored cortex of cloudy swelling. The suprarenals were not abnormal. The bladder reached midway to the umbilicus. The urine was straw-colored and acid, with a specific gravity of 1.009. There was a faint trace of albumin, but no sugar or acetone. Microscopically, there were a few casts, some pus and epithelium and great numbers of spermatozoa. The bladder wall and prostate were normal. Lymph nodes were taken from the axillae, neck, mesentery and groin. They were very small, the largest measuring only 1 cm in diameter. The nodes were soft and pink, indicating loss of lymphoid cells rather than hyperplasia. The bone marrow of the femur was fatty. Here and there were reddish specks, but no definite extravascular blood could be detected. The marrow of the vertebrae, calvarium and ribs was slightly more pink, but also extremely fatty. The brain weighed 1,590 Gm. There were numerous large subpial hemorrhages over the cortex, and the cerebellum was speckled with petechiae. Free blood appeared in the subarachnoid space. A colon bacillus was cultured from the heart's blood.

Microscopic Examination.—Sections of the heart revealed marked hemorrhage into the myocardium. The muscle fibers were separated by edema, and many of them were hydropic. In the lungs, alveoli were plugged with fibrin

but contained no inflammatory cells. This fibrin was loaded with bacilli and cocci. The remaining alveoli showed a granular precipitate indicating edema. The spleen contained a considerable amount of hemosiderin, some of which was within mononuclear cells. Sections of the liver showed hydropic degeneration and edema. There were areas of necrosis in which the liver cells stained diffusely with eosin, and some were entirely disintegrated, but there was no inflammatory cell infiltration. Bacteria were also found in these areas. The suprarenals showed areas of focal necrosis. The remaining cells contained little lipoid. The kidneys were normal except for a granular appearance in the tubular epithelium. The testicles showed edema and only a few epithelial cells lining the seminiferous tubules. The lymph nodes were small, and had the normal architecture. The sinuses were large, and the cords were made up of discrete, scattered lymphoid cells. The bone marrow consisted chiefly of fat with few widely scattered cells. Some of these which contained an abundant cytoplasm and a small nucleus showed inclusions of hemosiderin and were probably of endothelial origin. Others were large and had practically an equal amount of nucleus and nongranular cytoplasm. The nuclei of the latter contained large chromatin granules. No mitotic figures nor nucleated reds were seen. From the phagocytosed pigment it seemed that endothelial cells were as numerous as any other type of cell in the bone marrow.

COMMENT

In 1897, Santesson [1] reported nine cases of benzene poisoning in young women who were working with benzene rubber cement in a tire factory. The symptoms were those of purpura hemorrhagica with hemorrhages from the mouth, nose, stomach and uterus. The number of red blood cells was greatly reduced, and there was marked leukopenia. Four of the nine patients died after exposures which varied from three weeks to four months. Selling [2] reported similar cases in 1911. His experiments on rabbits intoxicated with benzene seemed to warrant concluding that there was a destruction of adult erythrocytes and leukocytes with a decrease or lack in the formation of new elements. The injury to the erythroblastic tissue was the last to appear and the last to disappear. Duke [3] found a marked diminution in the number of circulating platelets and an almost complete disappearance of megacaryocytes from the bone marrow. Winternitz and Hirschfelder [4] observed that rabbits treated with benzene had little resistance to pneumonia, and that the pneumonic exudate contained few inflammatory cells. Rusk [5] states: "Benzol intoxicated rabbits produce hemolysins and precipitins

1. Santesson: Arch. f. Hyg. **31**:336, 1897.

2. Selling, L.: Benzol Als Leukotoxin, Beitr. z. path. Anat. u. Path **51**: 576, 1911.

3. Duke, W. W.: Causes for Variations in the Platelet Count, Arch. Int. Med. **11**:100, 1913.

4. Winternitz, M. C., and Hirschfelder, A. D.: Studies Upon Experimental Pneumonia in Rabbits, J. Exper. Med. **17**:657, 1913.

5. Rusk, G. Y.: The Effect of Benzol Intoxication and Consequent Leucopenia on the Formation of Artificial Hemolysins and Precipitions, Univ. Calif. Pub. in Path. **2**:139-145, 1914.

much less efficiently than normal animals." During the late war, benzene manufacturing plants were first established in this country, the product being a necessity in the manufacture of explosives. Since the war, these plants have put benzene on the market, and it is being used in a great many industries as a solvent where formerly the relatively nontoxic petroleum distillates were employed. The importance of benzene in industrial medicine has been well summed up by Alice Hamilton.[6]

The diagnosis in this case was evident when the patient came to us. He was aware of his exposure to benzene, and findings more typical or more in agreement with those of reported cases could hardly have been devised. The only unusual thing was the negative constrictor test for petechial hemorrhages in the presence of unprovoked petechiae and other findings typical of hemorrhagic purpura. The test was not repeated, and therefore cannot be termed conclusive. There was little need for elaborate differential diagnosis. Purpura hemorrhagica secondary to sepsis was excluded because the fever in our case was a late event, and the infection was obviously secondary. Aleukemic leukemia of the acute type did not seem likely; first, because there was no demonstrable lymphoid hyperplasia; second, because there was a larger percentage of granular cells than one usually sees in such leukemia; and third, no pathologic or immature cells appeared in the blood. The differential blood count was of special interest. It showed a marked decrease, both relative and absolute, in cells of myelocytic origin. Lymphocytic cells were relatively increased, but there was a marked decrease in absolute numbers. The large mononuclears and "transitionals" which are collectively termed endothelial leukocytes were relatively increased, but the absolute number was within normal limits. It seems from this fact, as well as from the histologic study of the bone marrow, that endothelial cells are the only circulating elements to withstand the toxic action of benzene. Indirectly this may be taken as further evidence of the already well established fact that large mononuclears and "transitionals" are of endothelial origin.

The action of benzene is generally appreciated because of its former use in the treatment of myelogenous leukemia. The difficulties encountered in the control of dosage and the simultaneous toxic action of the leukopoietic, erythropoietic and platelet forming systems have led many to discontinue its use as a therapeutic agent. Variation in personal susceptibility to benzene seems to be marked, and clinical observations show that the toxic action continues for a considerable period after withdrawal of the drug. One of our many patients with myelogenous leukemia treated with small doses of benzene in which the drug was

6. Hamilton, Alice P.: The Growing Menance of Benzene, J. A. M. A. **78**: 627, 1922.

discontinued when the white blood count was still 30,000 clearly shows its progressive action. The white cells continued to fall until there was an almost complete leukopenia. A profound anemia soon developed, and the patient died with all the symptoms of purpura hemorrhagica. A progressive poisoning is also shown in the case here reported. His last exposure to benzene was on March, 1925, several weeks before any symptoms of purpura developed, and death occurred on June 7, more than eleven weeks after his withdrawal from the drug.

Two outstanding feature were presented at necropsy, namely: a marked hematopoietic insufficiency and a decided lack of response to infection. The hematopoietic insufficiency was extreme. A considerable percentage of the few cells present in the bone marrow contained inclusions of pigment and were obviously endothelial phagocytes. The remaining cells were about the size of myelocytes but were nongranular. No megacaryocytes were seen, and no evidence of active formation of either red or white blood cells could be determined. The lymphoid system appeared somewhat less disturbed. The lymph nodes were small with a paucity of lymphocytes. Prussian blue reaction applied to the liver, heart and kidneys showed no definite increase in iron pigment. This seems to show that the action of benzene is more marked on the cells of the blood-forming tissue than on the adult circulating elements. Myelocytic cells and megacaryocytes were most affected, lymphoblastic tissue to a less degree, while the endothelial elements were not especially damaged. Purpuric manifestations were perhaps an evidence of physiologic disturbance in the endothelial cells of the capillaries. The septicemia, which was a rather late event, and which showed localization of the infectious agent in the liver, lungs and suprarenals was extremely interesting. The lung condition resembled, in the gross, an extensive bronchopneumonia. Microscopically, however, the picture was not that of an ordinary pneumonia. No inflammatory cells were present, although the alveoli were plugged with fibrin which contained numerous organisms. The liver showed areas of focal necrosis in which there were an abundance of organisms, but no inflammatory cells.

SUMMARY

The case reported though complete in presenting all of the features so far recognized, adds nothing that is new, except possibly the relative immunity of endothelial leukocytes in benzene poisoning and the absence of evidence of adult erythrocyte destruction. The necropsy also confirms the morbid anatomic changes described in animals. The established facts in chronic benzene poisoning are included in the following list: leukopenia, aplastic anemia, thrombocytopenia, aplasia of the bone marrow, absence of inflammatory cell response to infection. The history of exposure to benzene in this case has been verified, thus making the chain of evidence complete.

PRESERVATION AND TRANSPORTATION OF BLOOD FOR CHEMICAL STUDY*

HENRY J. JOHN, M.D.

CLEVELAND

It has always been difficult for general practitioners located at a distance from clinical laboratories to secure adequate chemical data on the blood of their patients. The chief difficulty has been due to the lack of a convenient and efficient receptacle. With this need in view, three years ago I devised a special collecting tube containing picric acid in suitable solution to kill the ferment in the blood, and at the same time to precipitate the proteins.[1] There are some objections, however, to the use of picric acid by certain workers who prefer using the Folin Wu method.

Potassium oxalate cannot properly be used as a preservative as the decomposition of the blood sugar to carbon dioxide and water goes on continuously so that after a certain period of time and at a certain temperature much or nearly all of the sugar may be lost from such a specimen of blood.[2] It is necessary therefore to use a preservative which will give the same values at the time of the examination of the specimen as would have been obtained at the time the specimen was taken from the patient. It follows that for any apparatus to be used for the transportation of blood for blood chemistry studies the following features are essential: (1) It must contain an adequate preservative. (2) The method of use must be simple and foolproof.

During the last few years a good many investigators have been working on this problem; the principal contributions in this field are given in the list of references and are summarized briefly in table 1.

The data of these various authors therefore appear to show that either sodium or potassium fluoride is the preservative of choice. Formaldehyde is effective, but it introduces an error, as the result of which, according to Bock,[3] the blood sugar readings are too high.

My studies on the subject are best summarized in the accompanying graphic charts and tables. An examination of figure 1 shows clearly that in blood which is preserved by potassium oxalate a fairly uniform rate of glycolysis takes place which indicates at once that this chemical

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* From the Cleveland Clinic.

1. John, H. J.: Methods of Precision in the Diagnosis of Diabetes: A Special Instrument, J. A. M. A. **78**:103-105, 1922.

2. John, H. J.: Glycolysis, Ann. Clin. Med. **3**:667-696, 1925.

3. Bock, J. C.: Formaldehyde for Preservation of Blood Specimens, J. Biol. Chem. **59**:73-76, 1924.

is inadequate. Furthermore, errors are introduced when large portions of oxalate are used.[4] Chart 1 shows also that when sodium fluoride is used there is no appreciable change in the blood sugar during the first twenty-four hours, after which a more or less marked glycolysis takes place.[5]

Figure 2 shows the findings in studies in which blood was preserved by means of a saturated solution of sodium fluoride (1 drop to 1 cc. of blood). It will be noted that in these studies the blood sugar level is uniform with practically no glycolysis.

Figure 3 shows the findings in studies of blood preserved with sodium fluoride (1 drop to 1 cc. of blood) and solution of formaldehyde

TABLE 1.—*Summary of Investigations of Different Preservatives of Blood as Reported in the Literature*

Author	Preservative Used	Result
1. Denis and Aldrich, 1920.....	Formaldehyde.....	Blood sugar constant for four days
2. Sander, 1923.....	Sodium fluoride and thymol (10:1) mg. per 5 cc. of blood	Sugar, urea, uric acid, creatinin, nonprotein nitrogen constant for from five to six days
3. Sweany, 1923.....	Phenol 65 mg. per 5 cc. of blood	Phenol interferes with use of picramic acid method of examination
4. Major, 1923.....	Potassium fluoride, saturated solution, 1 drop per 5 cc. of blood	Efficacious up to eight days
5. Bock, 1924.....	Formaldehyde.....	Too high values for blood sugar were secured by the use of commercial solution of formaldehyde
6. Denis and Beven, 1924.....	Sodium fluoride, 60 mg. per 10 cc. of blood	Sugar, urea, creatinin, uric acid, constant for 96 hours, nonprotein nitrogen constant only for 48 hours
7. Randles and Grigg, 1924.....	Trace of formaldehyde (dipping a toothpick in the solution and then stirring in the blood)	Preserves blood for from two to three days
8. Cameron and Williamson, 1925	Sodium fluoride and thymol (10:1) mg. per 5 cc. of blood	Sugar, creatinin, urea, nonprotein nitrogen remain unaltered for three or four days; uric acid rapidly decreases

(1 drop to 5 cc. of blood). It will be noted that there is practically no glycolysis during a period of forty-eight hours.

Figure 4 shows the findings in comparative studies of blood sugar changes in the same specimen of blood preserved by two methods, namely: (*a*) sodium fluoride (1 drop to 1 cc. of blood) and solution of formaldehyde (1 drop to 5 cc. of blood), and (*b*) potassium oxalate (30 mg. to 10 cc. of blood) and solution of formaldehyde (1 drop to 5 cc. of

4. John, H. J.: The Effect of Potassium Oxalate on Blood Sugar Determinations, J. Lab. & Clin. Med. **10**: 1000-1004, 1925.

5. All my blood sugar determinations were made by the Myers-Bailey method.

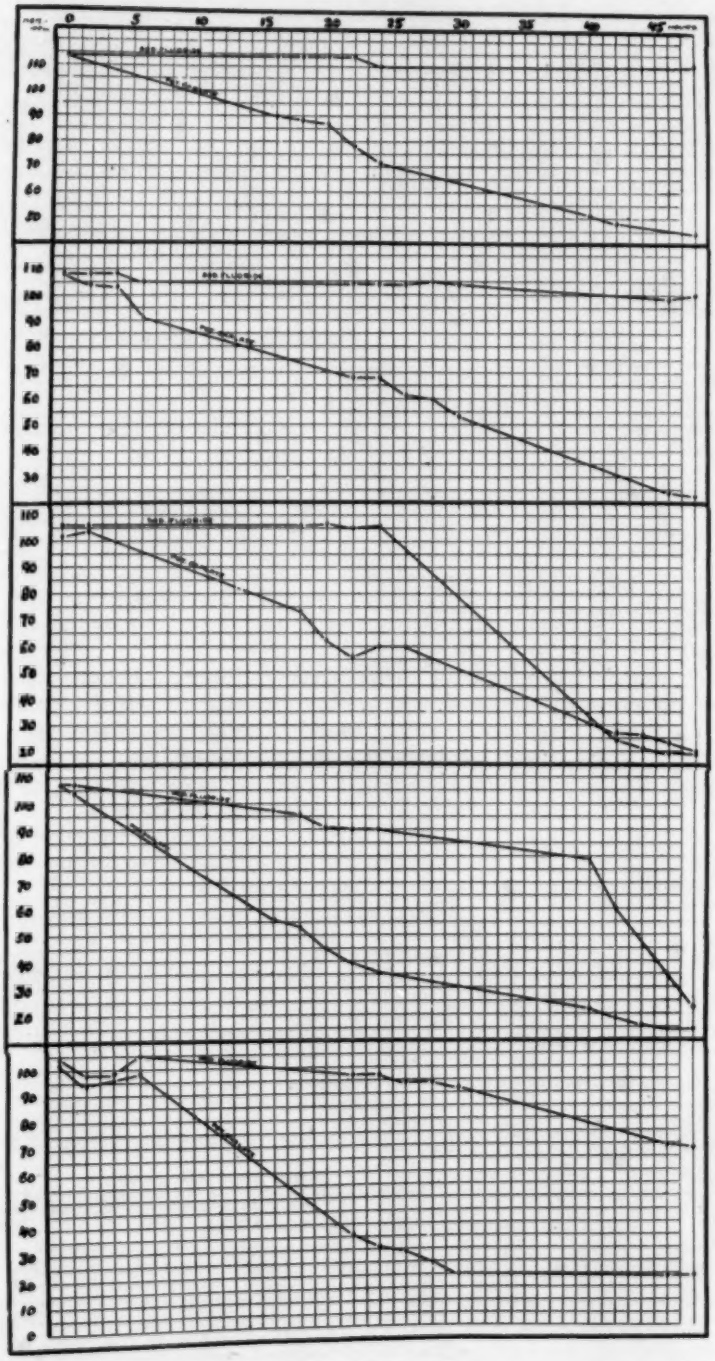

Fig. 1.—Findings in comparative studies of blood sugar changes in blood preserved with sodium fluoride and in blood preserved with potassium oxalate.

TABLE 2.—*Rate of Glycolysis in Blood in the Presence of Potassium Oxalate, 30 mg. Per Ten Cubic Centimeters of Blood, and Sodium Fluoride, Saturated Solution, 1 Drop to Each 1 cc. of Blood (Room Temperature)*

Sample No.		Blood Sugar, Mg. per 100 Cc.											
		0 Hr.	1 Hr.	16 Hr.	18 Hr.	20 Hr.	22 Hr.	24 Hr.	40 Hr.	42 Hr.	44 Hr.	46 Hr.	48 Hr.
1	Potassium oxalate	107	104	56	53	45	39	36	22	18	16	14	14
	Sodium fluoride	107	107	97	96	91	90	90	79	60	..	..	22
		Blood Sugar, Mg. per 100 Cc.											
		0 Hr.		16 Hr.	18 Hr.	20 Hr.	22 Hr.	24 Hr.	40 Hr.	42 Hr.	44 Hr.	46 Hr.	48 Hr.
2	Potassium oxalate	114	...	90	88	87	78	72	51	48	..	..	44
	Sodium fluoride	114	...	114	114	114	114	110	110	110	110	110	111
		Blood Sugar, Mg. per 100 Cc.											
		0 Hr.		2 Hr.	18 Hr.	20 Hr.	22 Hr.	24 Hr.	26 Hr.	42 Hr.	44 Hr.	46 Hr.	48 Hr.
3	Potassium oxalate	102	...	104	73	62	56	60	60	27	26	23	20
	Sodium fluoride	106	...	106	106	107	105	106	..	24	21	19	19
		Blood Sugar, Mg. per 100 Cc.											
		0 Hr.		2 Hr.	4 Hr.	6 Hr.	22 Hr.	24 Hr.	28 Hr.	28 Hr.	30 Hr.	46 Hr.	48 Hr.
4	Potassium oxalate	102	...	94	96	98	36	31	29	25	20	19	19
	Sodium fluoride	104	...	98	98	105	97	97	94	94	92	69	68

TABLE 3.—*Rate of Glycolysis in Blood in the Presence of Potassium Oxalate, 30 mg. per 10 cc. of Blood, and Sodium Fluoride, Saturated Solution, 1 Drop to Each 1 cc. of Blood, Plus 1 Drop of Formaldehyde in Each Specimen (Room Temperature)*

Sample No.		Blood Sugar, Mg. per 100 Cc.										
		0 Hr.	2 Hr.	4 Hr.	6 Hr.	22 Hr.	24 Hr.	26 Hr.	28 Hr.	30 Hr.	46 Hr.	48 Hr.
1	Potassium oxalate	108	104	103	91	68	68	61	60	53	24	23
	Sodium fluoride	108	108	108	105	104	104	104	105	104	98	100
		Blood Sugar, Mg. per 100 Cc.										
		0 Hr.	2 Hr.	18 Hr.	20 Hr.	22 Hr.	24 Hr.	26 Hr.	42 Hr.	44 Hr.	46 Hr.	
2	Potassium oxalate	106	95	91	91	91	80	80	80	79	70	
	Sodium fluoride	104	104	104	104	104	103	103	103	103	103	
		Blood Sugar, Mg. per 100 Cc.										
		0 Hr.	2 Hr.	18 Hr.	20 Hr.	22 Hr.	24 Hr.	26 Hr.	42 Hr.	44 Hr.	46 Hr.	48 Hr.
3	Potassium oxalate	132	116	126	126	126	112	111	111	111	110	108
	Sodium fluoride	134	125	132	132	131	117	113	113	114	112	112
		Blood Sugar, Mg. per 100 Cc.										
		0 Hr.	2 Hr.	4 Hr.	6 Hr.	22 Hr.	24 Hr.	26 Hr.	42 Hr.	44 Hr.	46 Hr.	48 Hr.
4	Potassium oxalate	92	92	90	79	76	76	..	..	..	63	63
	Sodium fluoride	91	91	90	85	77	78	..	..	..	71	71
		Blood Sugar, Mg. per 100 Cc.										
		0 Hr.	2 Hr.	18 Hr.	20 Hr.	22 Hr.	24 Hr.	26 Hr.	42 Hr.	44 Hr.	46 Hr.	48 Hr.
5	Potassium oxalate	111	106	104	94	94	94	..	..	83	..	83
	Sodium fluoride	111	111	98	98	98	97	..	..	94	..	94

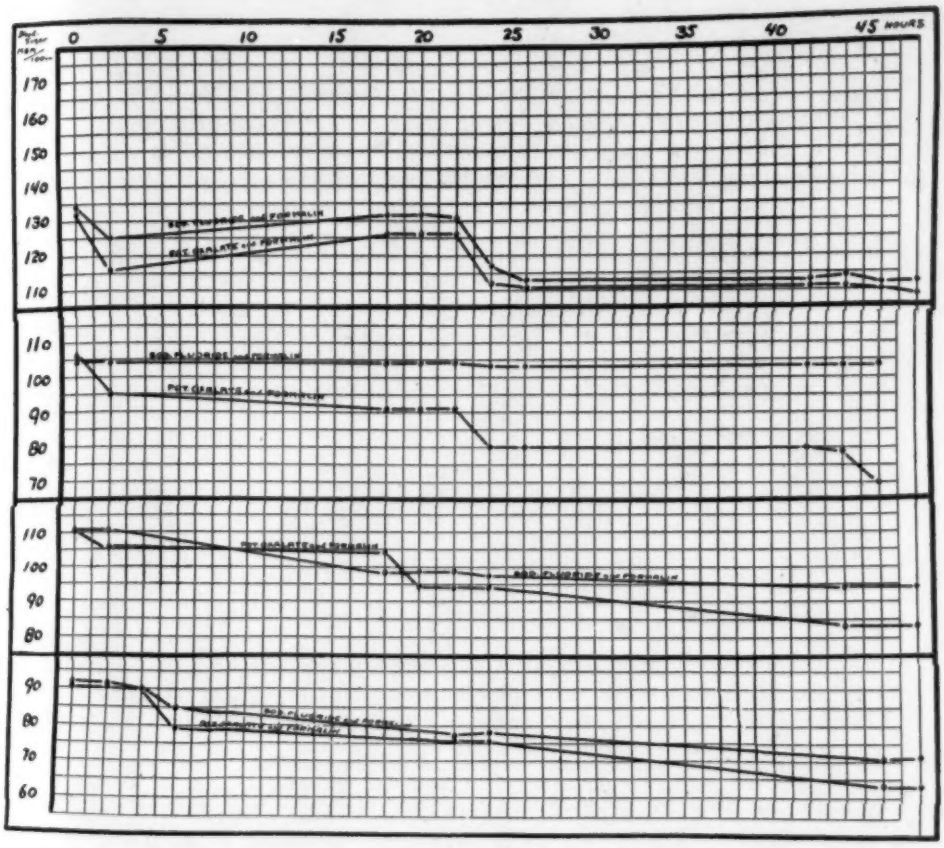

Fig. 2.—Rate of glycolysis in blood preserved with potassium oxalate-formalin and sodium fluoride-formalin.

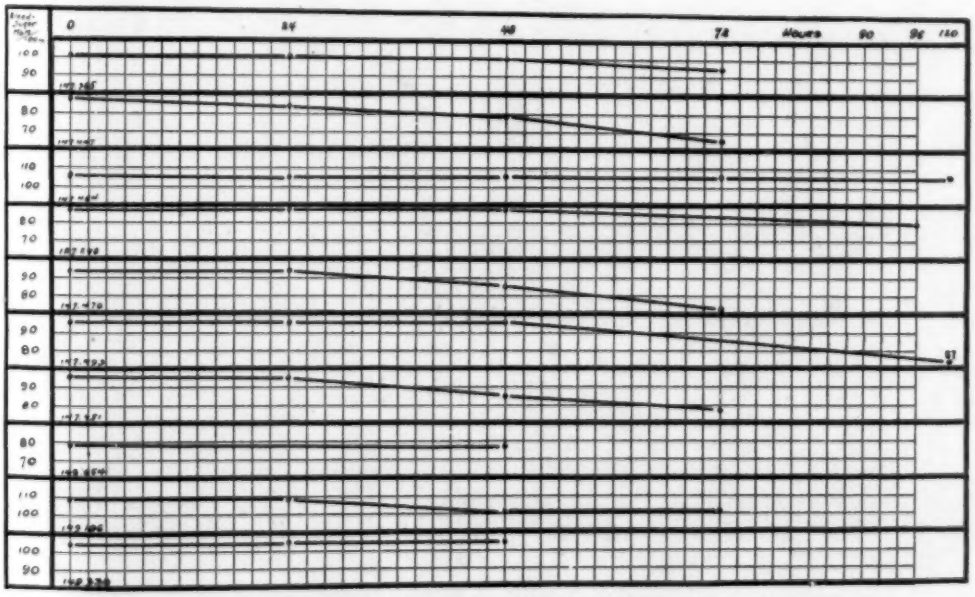

Fig. 3.—Findings in blood preserved with a saturated solution of sodium fluoride.

TABLE 4.—*Rate of Glycolysis in Blood in the Presence of Sodium Fluoride, 1 Drop Saturated Solution to 1 cc. of Blood and Formaldehyde, 1 Drop to 5 cc. of Blood*

Time in Hours	Blood Sugar, Mg. per 100 Cc.					Time in Hours	Blood Sugar, Mg. per 100 Cc.				
	Specimen 1	Specimen 2	Specimen 3	Specimen 4	Specimen 5		Specimen 1	Specimen 2	Specimen 3	Specimen 4	Specimen 5
0	261	112	118	108	118	51	...	...	105	...	...
2	...	112	...	...	...	52	...	...	...	...	103
3	...	...	118	...	...	55	...	...	105	...	...
4	...	...	...	...	116	64	...	...	...	97	...
6	261	...	...	...	...	68	...	...	...	97	102
7	...	...	118	...	...	70	...	111	...	...	...
16	...	...	...	108	...	71	...	...	105	...	...
18	...	111	...	...	...	72	...	...	...	97	102
20	...	...	...	107	107	75	...	...	105	...	...
22	...	111	...	...	...	76	...	...	...	...	102
23	...	...	114	...	...	79	...	...	107	...	...
24	261	...	...	105	107	82	...	...	...	...	102
26	...	111	...	...	...	86	...	...	...	...	102
27	...	...	114	...	...	92	...	...	...	97	...
28	...	...	...	...	107	94	...	111	...	...	...
30	261	...	...	...	...	96	187	...	...	...	...
31	...	...	114	...	...	99	...	...	105	...	...
40	...	...	...	97	...	102	82	...	...	...	...
44	...	...	...	97	103	118	...	111	...	...	...
46	...	111	...	...	...	120	26	...	...	...	...
47	...	...	104	...	...	126	24	...	...	...	...
48	261	...	...	97	103	143	...	...	105	...	...
50	...	111	...	...	...	144	24	...	...	...	...

TABLE 5.—*Rate of Glycolysis in Blood in the Presence of Sodium Fluoride, Saturated Solution, 1 Drop to Each Cubic Centimeter of Blood (Room Temperature)*

	Blood Sugar, Mg. per 100 Cc.												
	0 Hr.	2 Hr.	18 Hr.	22 Hr.	26 Hr.	42 Hr.	46 Hr.	50 Hr.	66 Hr.	70 Hr.	74 Hr.	98 Hr.	118 Hr.	146 Hr.
Specimen 1	118	113	100	100	100	100	100	100	100	97	..	..	..	27
Specimen 2	87	87	81	81	80	80	80	80	77	77	77	77	20	

TABLE 6.—*Rate of Glycolysis in Blood in the Presence of Sodium Fluoride, Saturated Solution, 1 Drop to Each Cubic Centimeter of Blood (Room Temperature)*

	Blood Sugar, Mg. per 100 Cc.					
	0 Hour	24 Hours	48 Hours	72 Hours	96 Hours	120 Hours
Specimen 1	101	101	100	94	..	..
Specimen 2	88	83	79	63	..	..
Specimen 3	106	105	105	105	..	..
Specimen 4	88	88	88	...	..	80
Specimen 5	93	93	84	...	72	..
Specimen 6	96	96	96	...	57	..
Specimen 7	96	95	84	77	..	..
Specimen 8	79	...	77	...	..	..
Specimen 9	109	109	101	101	..	..
Specimen 10	105	105	105	...	..	..

blood). These studies show the greater effectiveness of the first of these methods although there is a gradual glycolysis after the first twenty-four hours.

Table 7 shows the constancy of values when quantities of 10 to 50 mg. of sodium fluoride are used in combination with thymol (one part

TABLE 7.—*The Effect of Varying Amounts of Sodium Fluoride and Thymol (Dry Powder) (10: 1) on Blood Sugar (Room Temperature)*

	Blood Sugar, Mg. per 100 Cc.				
	In 10 Mg. Sodium Fluoride	In 20 Mg. Sodium Fluoride	In 30 Mg. Sodium Fluoride	In 40 Mg. Sodium Fluoride	In 50 Mg. Sodium Fluoride
Specimen 1	129	127	143	...	...
Specimen 2	101	101	103	101	101
Specimen 3	96	96	94	93	93
Specimen 4	115	115	115	115	113
Specimen 5	121	117	121	121	98
Specimen 6	113	113	113	113	113

TABLE 8.—*Determination of the Amount of Blood Which 15 mg. of Sodium Fluoride and Thymol (Dry Powder) (10: 1) Will Keep From Clotting*

	Blood Sugar, Mg. per 100 Cc.					
	In 2 Cc. Blood Volume	In 4 Cc. Blood Volume	In 6 Cc. Blood Volume	In 8 Cc. Blood Volume	In 10 Cc. Blood Volume	In 12 Cc. Blood Volume
Specimen 1	...	...	...	105	...	...
Specimen 2	...	...	...	...	...	Clotted
Specimen 3	...	...	...	...	Clotted	...
Specimen 4	...	...	105	...	...	...
Specimen 5	...	...	...	91	...	...
Specimen 6	167	167	...	...	...	...
Specimen 7	...	...	...	Clotted	...	...
Specimen 8	...	...	...	148	...	...
Specimen 9	...	...	111	...	...	...
Specimen 10	...	...	...	Clotted	...	...
Specimen 11	...	...	...	...	Clotted	...

TABLE 9.—*Determination of the Amount of Blood Which 20 mg. of Sodium Fluoride and Thymol (Dry Powder) (10: 1) Will Keep From Clotting*

	Blood Sugar, Mg. per 100 Cc.			
	In 8 Cc. Blood Volume	In 10 Cc. Blood Volume	In 12 Cc. Blood Volume	In 15 Cc. Blood Volume
Specimen 1	107	...	...	...
Specimen 2	...	...	113	...
Specimen 3	...	...	...	Clotted
Specimen 4	...	...	Clotted	...
Specimen 5	...	101	...	...
Specimen 6	...	...	102	...
Specimen 7	...	...	96	...

in 10), as suggested by Sander in 1923; according to this author constant values can be obtained for a period of from 5 to 6 days not only for sugars, but for urea, uric acid, creatinin and nonprotein nitrogen.

Tables 8 and 9 show the volume of blood which 15 and 20 mg. of the 10: 1 sodium fluoride-thymol (dry powder) mixture will keep from

clotting. For 10 cc. of blood, which is sufficient for all routine examinations of the principal metabolites in the blood, 20 mg. is sufficient. If large volumes of blood are desired, this amount must of course be increased.

It is often desirable to measure not only the blood sugar content but also the amount of urea, uric acid and nonprotein nitrogen, etc., in the blood as in cases of nephritis or other renal diseases. Blood preserved with the fluoride-thymol (dry powder) mixture can be used to secure accurate estimates of the amount of any one or of all metabolites in a specimen of blood even if it has to be transported to the laboratory through the mail so that the examination is delayed for one or two days. For the transportation of blood it is obviously essential to provide a

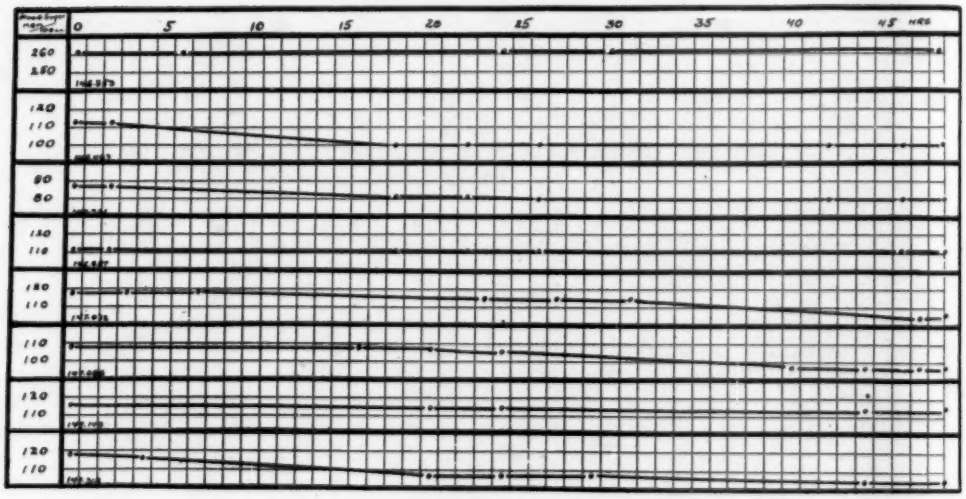

Fig. 4.—Findings in blood preserved with sodium fluoride and solution of formaldehyde.

receptacle which will contain a sufficient amount of the preservative to make possible the securing of the sample with a minimum expenditure of time. A tube has therefore been devised,[6] constructed on the principle of the Keidel tube, with vacuum suction, which contains a sufficient amount of the fluoride-thymol (dry powder) mixture to prevent the blood from clotting and from decomposition. After applying a tourniquet to the arm and sterilizing the skin with alcohol, the glass tube which protects the sterile needle and the stylet is removed, and the needle is inserted into the vein. When the operator is certain that the needle is within the vessel, the end of the sealed tube is crushed with a hemostat, as indicated in the illustration (figure 5), and the suction of

the vacuum draws the blood inside the tube. When a sufficient amount has been secured, the needle is pulled out of the vein, the tourniquet first having been released, and the tube is slightly agitated in order to insure complete mixing of the chemicals with the blood; the stylet is reinserted and the glass tube placed over the needle. The specimen is then ready to be mailed to the laboratory. This tube is of value to the physician who does not have ready access to a laboratory and to the laboratory clinician, as a sample of blood can be secured in any case without delay. Furthermore, this not only provides an easy method for securing the specimen but any blood chemistry technic can be used with specimens preserved in this manner, so that the internist can employ or have employed his method of choice.

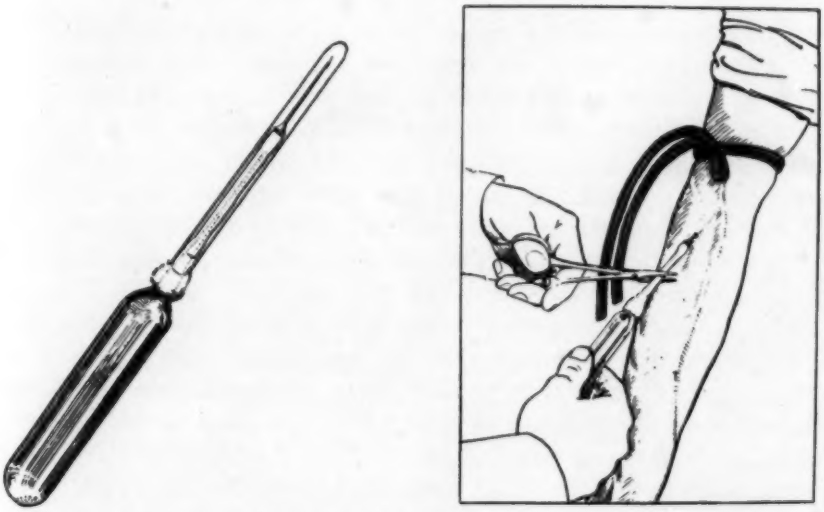

Fig. 5.—*A*, vacuum tube for collecting blood for chemical studies; *B*, method of procedure.

Some of the insurance companies are now beginning to request blood sugar studies, and soon they will undoubtedly be asking also for blood urea studies in order to evaluate their risks; this easy manner of collecting blood will be of great value to insurance examiners.

SUMMARY

A vacuum tube has been devised for collecting, preserving and mailing blood samples. The vacuum tube contains 20 mg. of fluoride thymol mixture (10:1), which will prevent 10 cc. of blood from clotting, and maintain the blood sugar at its original level. This makes it

6. Manufactured by Hynson, Westcott & Dunning, Baltimore.

possible to send blood specimens to more or less distant laboratories for examination and obtain reliable results.

NOTE.—Since the writing of this article a slight change has been instituted in the blood chemistry tube. A small piece of glass tubing is inserted in the middle of the rubber tubing so that the blood may be seen when it appears in the tube. In this way, the vacuum is not broken inadvertently before the blood enters the tube. Furthermore, even if the vacuum has been broken, it can be restored and the tube used again by clamping the rubber tube with a hemostat before the needle is withdrawn from the tissues.

Another point of interest which has recently been elicited is the fact that even 150 mg. of the fluoride-thymol mixture does not alter the blood sugar figures.

General Review

THE REACTIONS OF MITOCHONDRIA TO CELLULAR INJURY *

E. V. COWDRY
NEW YORK

Before attempting to discuss the reactions of mitochondria to cellular injury, brief mention may be made of certain points definitely known regarding their nature.

THE PROPERTIES OF MITOCHONDRIA [1]

1. Mitochondria are usually of rather low refractive index, but nevertheless, under favorable conditions, they may often be seen in living cells by direct illumination without the addition of any coloring matter. They are clearly revealed by dark-field examination.

2. They occur in the form of granules, rods and filaments, and occasionally of networks which vary in size and shape. In length the filaments rarely exceed the diameter of a red blood corpuscle (7.5 microns), and are usually much shorter; in diameter they vary from 0.5 to 1 micron. They are of fluid consistency and readily change their shape in response to altered intracytoplasmic conditions.

3. They exhibit a characteristic color reaction, which is marked in animals and less so in plants, when Janus green B (diethylsafraninazodimethylanilin) is applied to living cells in physiologic sodium chlorid in a dilution as weak as 1 : 500,000. At first they assume a bluish-green color, which, on reduction, turns pink (diethylsafranin), and finally bleaches to a colorless leukobase. The delicacy of this reaction is indicated by the fact that Janus green (Grübler) and Janus green C will not color them specifically, although these dyes differ only in the substitution of an hydrogen and $(CH_3)_2$ group in place of the $(C_2H_5)_2$ group present in Janus green B. That the specificity is not due to the presence of the dimethylanilin group in the molecule is shown by the fact that Janus blue, in which the dimethylanilin is replaced by beta naphthol, will color the mitochondria with equal brilliancy (Cowdry, 1918).

4. They are easily destroyed by fixatives containing alcohol, ether, chloroform and similar reagents, and may be stained after appropriate fixation by the methods of Altmann, Benda, Bensley and others.[2]

* From the Rockefeller Institute for Medical Research, New York.

1. The term "mitochondria" (thread granules) is derived from the Greek μίτος, a thread, and χόνδρος, a grain, and was first introduced by Benda in 1898.

2. For technic see eighth edition of Lee's "Vademecum," edited by Gatenby, Philadelphia, P. Blakiston's Son & Company, 1921.

5. They are widely distributed in both plants and animals, but they are not omnipresent in living protoplasm, as some investigators have claimed or suggested.

6. They are not composed of a single chemical substance, but of a combination in varying proportions of protein and lipoid (Giroud, 1925). The precise nature of these components is unknown. There is no reason to believe that the same protein or the same lipoid is always involved. Beyond question the properties of mitochondria vary within certain limits, chiefly in respect to visibility in the living state, physiologic behavior, morphology, solubility and staining reactions. This variation may be partly explained by the real differences which exist in the character of the cytoplasm in which the mitochondria are embedded.

MITOCHONDRIA AS INDICATORS OF CELLULAR INJURY

With this information in mind, it is easy to understand how the belief originated that the study of mitochondria would open a new chapter in cellular pathology. It was thought that since they differ so radically from the nucleus, they would serve as indicators of entirely different types of pathologic change; further, that owing to their presence in the cytoplasm they would respond more quickly and readily than the nucleus in the manifold adjustments which are constantly taking place between living cells and their changing environments.

LITERATURE ON PATHOLOGIC CHANGES IN MITOCHONDRIA

An investigator wishing to learn what has already been done on some special topic will encounter many difficulties. He will find that papers dealing with mitochondria are not all of recent date, but that they are, on the contrary, scattered through the literature for a period of at least forty years. At Leipzig and in other parts of Germany, between 1880 and 1895, a considerable number of studies were made of mitochondria, under the heading of "Bioblasts," in cloudy swelling and other pathologic states. These investigations took their origin in Altmann's remarkable researches, and shared in the skepticism which his theoretical views invoked. They came at a time when the nucleus monopolized attention, owing partly to the discovery of its rôle in heredity. The aim in making up fixatives was to show nuclear detail. For this purpose, mixtures containing alcohol, chloroform or acetic acid were employed because of their rapid penetration. These substances destroyed the mitochondria, so that the more attention there was focused on the nucleus, the less chance there was for the detection of mitochondria.

It is to the pathologist, Benda, that the principal credit is due for directing the tide of interest back again to the cytoplasm. After a more critical appraisal of the fundamental significance of Altmann's discovery

that mitochondria occur in almost all protoplasm, a literature has developed which in its extent and varied character is without parallel in the history of cytology. Botanists, zoologists, anatomists, physiologists, pathologists and clinicians have studied them somewhat hurriedly and from different points of view. There has been no hesitancy in the introduction of new terms to indicate theoretical interpretations, morphologic characteristics and a whole host of observed and supposed properties, so that in practice one has to seek information under many synonyms and partial synonyms.

In the older literature descriptions of mitochondria occur under the following headings: bioblasts, or Altmann's granules, microsomes, interstitial granules, pseudochromosomes, fuchsinophile granules, plasmosomes, Schridde's granules, and others; but these terms have been used loosely, so that only some of the bodies referred to may properly be classed as mitochondria.

In the newer literature the term "mitochondria" is widely used, but other designations are also employed, such as chondriosomes and plastosomes. This is, unfortunately, not all that has to be borne in mind, because special terminations are often added to these words to designate certain morphologic types of mitochondria. Thus, "chondriosome" is used as a generic term, to include all mitochondria; "chondriocont," to indicate rodlike mitochondria; "chondriome," to indicate the cellular content of chondriosomes, and so on (Cowdry, 1921).

Another deterrent is that many papers give important information regarding mitochondria without mentioning them specifically in their titles, so that unless much collateral reading is done, facts which may be significant are likely to be overlooked.

In view of these circumstances, the literature on mitochondria frequently has been reviewed more or less exhaustively. The most complete summary is that of Duesberg (1912), which covers all the available papers—about 500—from the beginning of work on the subject up to Oct. 15, 1911. In this, the behavior of mitochondria in development and inheritance is stressed. Another review, commencing at the time when Duesberg left off, and extending to July, 1923, has been published,[3] giving a synopsis of about 500 papers, the importance of mitochondria in cellular physiology and pathology being emphasized.

Up to the present time, however, there has been no attempt to sort out all the papers which relate specifically to the pathology of mitochondria, and to classify them so that the data on any subject may readily be secured. To do this effectively would be an almost impossible task, owing to the difficulty of drawing a sharp line of distinction between normal and abnormal cellular activities. Moreover, the technic

3. Section on mitochondria in a text-book on "General Cytology," University of Chicago Press, 1924.

used for the demonstration of the Golgi apparatus frequently reveals the mitochondria also—a fact to which we owe a considerable amount of supplementary information regarding the mitochondria in the pathologic states in which the Golgi apparatus has been investigated (Cowdry, 1924).

The following summary is presented as a guide to the literature, with full knowledge of its incompleteness.[4] The plan adopted of trying to focus all the available information bearing on pathologic changes in the mitochondria in each of the principal tissues has at least one obvious weakness. Take, for instance, the process of regeneration which has been studied in many tissues; to give the same reference over and over again would involve too much repetition, so that it is listed only under the headings of the principal cells involved. The same principle has been followed in other cases, which results in making the summary more concise and less complete.

Adenoids: hypertrophy, Alagna (1911, p. 27).

Blood Corpuscles: experimental anemia, Sappington (1918); gaseous inhalation, Kroop and May (1924); myeloblastic leukemia, Sabin, Austrian, Cunningham and Doan (1924).

Bone-Marrow: leukemia, Benda (1899), Klein (1910 *a* and *b*); inanition, Cunningham, Sabin and Doan (1924).

Cartilage: regeneration, Torraca (1914 *b*).

Choroid Plexus: status lymphaticus, epilepsy, meningitis, etc., Ciaccio and Scaglione (1913); war wounds, Grynfeltt (1918); death in different ways, Grynfeltt and Enzière (1913); ether and intravenous injection of distilled water, Weed (1923, p. 265).

Connective Tissue: inflammation, Dubreuil (1913, p. 138); regeneration, Romeis (1913).

Corneal Epithelium: vaccinia, Cowdry (1922).

Ependyma: death in different ways, Grynfeltt and Enzière (1919).

Epidermis: syphilitic chancre, edema, etc., Regaud and Favre (1912).

Gastro-Intestinal Epithelium: inanition, Ono (1920), Miller (1922); radiation, Beckton and Russ (1911).

Kidney Epithelium: anemic necrosis, Israel (1891, p. 310), Champy (1914, p. 61); diuresis, Pizzini (1908), Hjelt (1912), Mislawsky (1913), Policard (1910, p. 272), Mayer and Rathery (1907 a, b); anesthetics, Smith and Rettie (1925); diphtheric changes, Ciaccio (1913), Dibbelt (1914); long-continued hyperfunction of, Emge (1921); regeneration in uranium nephritis, Oliver (1916); fatty degeneration, Ophüls (1907), Lubarsch (1897); autolysis, Policard and Garnier (1905); phosphorus poisoning, Ciaccio (1913); hyaline granular degeneration, Fahr (1914); cloudy swelling, Schilling (1894, p. 470), Landsteiner (1903), Anitschkow (1914), Smith and Rettie (1925); in hemoglobinuria, Barratt (1913, p. 566); liver extirpation, Policard (1910, p. 245); radiation, Beckton and Russ (1911); phloridzin poisoning, Policard and Garnier

4. The literature on the effect of injury on the mitochondria of tissue cultures is discussed in detail by Lewis and Lewis (1924). A considerable amount of work has been done on pathologic changes in the mitochondria of plant cells for which reference may be made to Guilliermond (1919), and Mangenot (1921).

(1907); inanition, Sjöbring (1900), Takaki (1907), Suzuki (1912), Okuneff (1923); compensatory hypertrophy, Enderlin (1895), De Giacomo (1911), Hirsch (1910); acidosis, bronchitis, pneumonia, meningitis and tuberculosis, Smith and Rettie (1925); bacteria, diphtheria toxin and distilled water, Jessen (1925); diphtheria toxin, d'Agata (1913).

Liver: acidosis, anesthetics, bronchitis, pneumonia, meningitis, and tuberculosis, Smith and Rettie (1925); inanition, Sjöbring (1900), Mayer, Rathery, and Schaeffer (1914), Okuneff (1923); sulphonal poisoning, Grynfeltt and Lafont (1921 a-e); phosphorus poisoning, Fiessinger (1909), Ciaccio (1913), Mayer Rathery and Schaeffer (1914), Bang and Sjovall (1916); arsenic poisoning, Policard (1909), Fiessinger (1909), Bang and Sjovall (1916); chloroform poisoning and effect of gall, Bang and Sjovall (1916); diet, Noël (1923); hypertonic and hypotonic salt solutions, Bang and Sjovall (1916); precirrhosis, Noël and Rosier (1924); radiation, Beckton and Russ (1911); hydrogen-ion concentration, J. T. Scott (1925).

Muscle: regeneration, Torraca (1914 a), Romeis (1913), Anitschkow (1914, 1923).

Myocardium: acidosis, anesthesia, bronchitis, pneumonia, meningitis and tuberculosis, Smith and Rettie (1925).

Nervous System: hibernation and inanition, Rasmussen (1919, 1921); fatigue, Strongman (1917); experimental poliomyelitis, McCann (1918); axon section, Luna (1913); fatty changes, Biondi (1915); beri-beri, Clark (1914, p. 92), Ma (1925); herpetic encephalitis, Cowdry and Nicholson (1923); cortical irritation, Collin (1914, p. 592); tearing out of the axon and in dysentery, Marinesco and Tupa (1922); rabies, Goodpasture (1925); regeneration, Nageotte (1922, p. 190); Wallerian degeneration, Nageotte (1922, p. 270).

Nose: polypus, Benda (1899, p. 380).

Ovary: inanition, Russo (1910).

Pancreas: diabetes, Homans (1914, 1915); inanition, Miller (1922), Okuneff (1923); inanition and refeeding, Ma (1923, 1924); vitamin deficiency, Wakefield (1923); phosphorus poisoning, Ciaccio (1913), W. J. M. Scott (1916); bronchitis, pneumonia, meningitis and tuberculosis, Smith and Rettie (1925); radiation, Beckton and Russ (1911).

Pineal Body: castration, Ruggeri (1914).

Prostate: hypertrophy, Dominici (1913, p. 295).

Respiratory Epithelium: tumor-like overgrowths, Cowdry (1925, p. 336).

Retina: light and darkness, Busacca (1915).

Skin: rodent ulcer, Regaud and Favre (1912, p. 329).

Spleen: inanition, Okuneff (1923); pernicious anemia, Shipley (1915, p. 75); radiation, Beckton and Russ (1911).

Suprarenals: ovariectomy, Mira (1912, p. 43); roentgen-ray, Cottenot, Mulon and Zimmern (1912).

Testicles: inanition, Okuneff (1923).

Thyroid: adenoma, Goetsch (1916); hyperplasia and iodine involution, Seecof (1925); pathologic secretory phenomena, Key (1922), Bolt (1924); experimental conditions, Nicholson (1923 b).

Tonsils: hypertrophy, Alagna (1911, p. 27).

Tumors: Lubarsch (1897, p. 640), Murray (1906), Beckton (1909, a, b; 1910, a, b, c), Veratti (1909), Bensley (1910), Favre and Regaud (1911, 1913 a, b), G. Arnold (1912 a, p. 283), Regaud and Favre (1912), Porcelli-Titone (1914, p. 237), Rio Hortega (1914, p. 92), Goetsch (1916, p. 132), Da Fano (1921, p. 87), Sokoloff (1922), Grynfeltt and Forgue (1922), Wood and Hartman (1922), Pringosen (1922), Bolt (1924), Ludford (1924, a and b; 1925, a and b).

Vascular System: Rocky Mountain spotted fever, Nicholson (1923 a).

SOURCES OF ERROR

While many of the papers dealing with mitochondria in pathologic conditions are worthy of the highest praise, others have obviously been written without due appreciation of the practical difficulties to be faced in this line of work.

However precise the instructions may be, mitochondrial technic cannot properly be shifted onto the shoulders of the average technician. The methods require some adjustment to each tissue, and must be standardized by frequent repetition. Even a slight and apparently trivial deviation from routine will often produce unexpected and profound alterations in the mitochondria. Pinching the tissues with forceps or letting them dry slightly in the air will render them useless for accurate work. Much has been written about the necessity of taking them from the body immediately after death. This depends, naturally, on the rate of autolysis. It is essential with glands and less so with the nervous system. If the tissues cannot be preserved immediately, it is better to keep them in a refrigerator at about 40 F. than at body temperature.

Impatient to obtain, with as little delay as possible, data urgently needed regarding human disease, and believing that the mitochondria afford a short cut to this end, investigators have often contented themselves with the study of human tissues obtained at operation or at necropsy, in which adequate control is out of the question, for the reason that the same conditions can never be exactly duplicated. Those who would not trust themselves to apply properly new and delicate chemical tests without some knowledge of chemistry, have rashly attempted, with hardly any information concerning them, to use the mitochondria as indicators of cellular injury. In some cases they have employed one method of technic only, without ascertaining whether it is the best for the particular tissue studied. Unless a method of fixation and staining is carefully checked by the observation of similar cells supravitally colored with Janus green, there is a strong probability that it will reveal only a part of the mitochondrial content of the cells, and much will be lost, so that the observations from the outset may be incomplete. Conversely, it is equally important to control the study of living cells by the examination of fixed and stained preparations.

In the supravital staining of mitochondria, there is a time element to be considered. The maximum coloration is rarely attained in less than five or ten minutes, during which interval more or less endosmosis or exosmosis and some mechanical flattening is unavoidable. Moreover, since the dye is relatively toxic, preparations of this kind really give a sort of moving picture of the behavior of mitochondria, as cells are slowly dying and must thus be interpreted. On the other hand, the fixation of mitochondria by powerful coagulants, like Regaud's fluid, is almost instantaneous, at least in the case of the cells situated at the

surface of the tissue, and the time factor is therefore negligible. To place complete reliance on one or the other method of study is to court disaster. Both should be employed. There is always a danger that the mitochondria in the supravitally stained cells will have time to fragment partially and thus to lose their normal filamentous shape, although this may seldom occur when the dye is applied carefully.

It is possible that some contradictions may be explained on this basis. For example, Cunningham, Sabin and Doan (1924), who have studied only supravitally stained cells, remark on their inability to detect the fine filamentous mitochondria which Schridde found in myeloblasts by other methods. Whatever may be the truth concerning the mitochondria in these cells, it is not possible to point to any instance in which mitochondria have been stretched out into filaments through faulty technic.

Statements that mitochondria are absent in living cells capable of multiplication should be received with caution. This was claimed for the cells of malignant tumors by Beckton (1909) and disproved by Bensley (1910). The inability of some of the earlier writers to discover mitochondria in the youngest cells of the spermatogenic series was readily overcome by later investigators. The more recent failure of Sabin and her co-workers to find mitochondria in the "primitive reticular cells," from which they believe that the more highly differentiated blood cells which contain mitochondria arise, is interesting. If the mitochondria are really absent under normal conditions, and the genetic seriation is proved, it would indicate beyond peradventure that the mitochondria in the older cells arise de novo in the cytoplasm. A single established case of such a phenomenon would have a definite bearing on the doctrine of mitochondrial continuity, the significance of which is discussed by E. B. Wilson (1925).

The literature on mitochondria abounds in preliminary notes on special topics. At this stage it requires thorough knowledge of the literature and no little imagination to select for study some type of cellular injury in which the mitochondrial changes have not already been touched on. In this particular branch of cytology the cream has been skimmed, but it is of doubtful character. With few notable exceptions, the study of mitochondria has been a one man affair, and we are told that this method of advance in medical science is out of date, although it sometimes yields results of the greatest importance.

Much of the work on mitochondria has been narrowly conceived. These structures have, for instancce, usually been investigated alone and apart from most of the other cellular components—an unwarranted abstraction, because the cell itself is the ultimate and indivisible physiologic unit in health and disease. This action has led to unqualified statements that the mitochondria do this and that, while in reality the

physiologic processes under discussion are functions of the activity of the whole cell of which the mitochondria are merely a part. It would be logical to begin with the most simple modifications of cellular activity caused, for example, by reduction of blood supply, and to analyze these in all their bearings before proceeding to the more complex, and in doing so to employ experimental animals in which given conditions can be reproduced again and again for verification at will. A consistent cooperative program extending over a fairly long period is needed. In spite, however, of the inconsistencies in method of approach and the fragmentary character of much of the work, something has alreay been accomplished, although it may be difficult to find in the confused state of the literature.

FACTS ESTABLISHED CONCERNING THE RESPONSE OF MITOCHONDRIA TO INJURY

Three general modes of mitochondria reaction have been recognized—qualitative, quantitative, and topographical—which may occur singly or in combination.

(1) Qualitative Changes: By far the most delicate qualitative response consists of the breaking up of filamentous mitochondria into granules. It is so delicate that it is often produced through injury caused by faulty technic alone, a possibility which must always be guarded against. It occurs in cells which, after ordinary methods of technic, look perfectly normal. Recently Smith and Rettie (1925) have found that the mitochondria of certain parts of the kidney tubules, of the myocardium and other tissues are fragmented in this way after general anesthesia, which may explain much of the depression and functional disorder which often follow the administration of ether and chloroform. Similar changes occur in inanition, in the earliest phases of phosphorus poisoning and several other pathologic states.

Evidently the cytoplasmic conditions which are favorable to a filamentous type of mitochondria may be upset or modified by a variety of agents, so that this change to granules cannot be regarded as specific. It is not even known whether these different modes of injury act directly on the mitochondria or whether the morphologic changes in them are merely the visible expression of a long line of interdependent chemical reactions in the cytoplasm which are reflected by the mitochondria: the latter interpretation has more to commend it. Rarely does the reverse process, of the lengthening of mitochondria, occur in response to injury. Occasionally it is said that they stain less intensely (Marinesco and Tupa, 1923), but statements of this kind are difficult to prove.

Following fragmentation, three further qualitative modifications are likely to occur: (*a*) the granular mitochondria may go into solution and disappear, in which case we have a process called "chondriolysis,"

which is likewise encountered after many different types of injury; (*b*) the granular mitochondria may, as individuals, enlarge into droplets and disappear or else undergo fatty changes, so that the condition may merge insensibly into one of fatty degeneration; (*c*) the granules may first agglutinate in clumps. This is followed by fusion of the individual elements and the formation of large droplets which are changed into fat, as described by Scott (1916) in phosphorus poisoning.

(2) Quantitative Changes: Changes in the number of mitochondria—or, speaking more accurately, in the amount of mitochondrial material—are equally likely to be misleading. It is difficult actually to obtain a uniform fixation throughout a block of tissue even in small portions of a gland, such as the pancreas. The different ingredients of the fixative act simultaneously and in a balanced fashion only on the most superficial cells, and successively on those lying more deeply, so that the number and shape of the preserved mitochondria will often vary with the distance of the cells from the surface. Furthermore, unless the stain is differentiated to exactly the same extent, an illusory impression may easily be created of decrease or increase in mitochondria, as between the experiment and the control. Sections of equal thickness from both should be mounted side by side on the same slide.

With rare exceptions, the observations recorded in the literature are based merely on the general appearance of sections, and slight quantitative changes have been ignored owing to the difficulty of estimating them with precision. Few investigators have availed themselves of Thurlow's (1916, 1917) method of counting the mitochondria in unit areas, or have tried to improve on it. It is important in all cells, but particularly in gland cells, to bear in mind the changes in volume which the cells are constantly undergoing. Unless this is done, when a gland in which the cells are small, having perhaps just discharged their secretion, is compared with another the cells of which are large and distended, it may at first sight be thought to exhibit an increase in mitochondria, although the absolute amount of mitochondria may not have changed. Conversely, when the cells are large and distended, the mitochondria may appear reduced and actually be so, relative to the volume of cytoplasm, without any positive change relative to the cells themselves as units.

The same problem is encountered in muscle cells, which may be extended or contracted. Nerve cells also undergo less noticeable changes in size. It is, likewise, desirable that the accurate volumetric methods devised by Jackson for glands should be utilized in the quantitative study of mitochondria, as has been done by Rasmussen (1921).

A diminution in the amount of mitochondria is often encountered, but an increase above normal is comparatively rare. It has, however, been reported in the thyroid gland (Goetsch, 1916; Bolt, 1924, and

Seecof, 1925), in the islets of Langerhans of the pancreas during diabetes (Homans, 1915), in the kidney following the administration of phloridzin (Policard, 1910), in regeneration (Romeis, 1912, 1913; Torraca, 1914, a, b, c; Nageotte, 1922) and in other conditions. In tumors there is great variability in the number of mitochondria which it has not been possible, thus far, to correlate definitely with malignancy, or with any special modification of the growth mechanism. It is safe to assume that a decrease in mitochondria is indicative of a depression of functional activity, and that an increase, in the rare cases in which it has been proved to occur, points to heightened activity, unless it is accompanied by fatty changes in the manner already referred to.

(3) Topographical Changes: By contrast, alterations in the position of mitochondria within the cell are much less likely to result from imperfect technic. They have been recorded in several conditions. The peripheral margination, just beneath the cell membrane, reported by Grynfeltt and Lafont (1921 a-e), after sulphonal poisoning is particularly noteworthy. A grouping of mitochondria about the nucleus is often observed in tumor cells, and is generally, but not always, associated with a change in form.

An explanation of these displacements of mitochondria is lacking. In certain instances it is possible that the mitochondria may be entirely passive and that their change in position may result from the taking up of fluid, as suggested by Weed (1923) in the case of the cells of the choroid plexuses. We do know that in some cells and in normal conditions, the mitochondria move back and forth between the immediate vicinity of the nucleus and the most peripheral cytoplasm. What is accomplished by this action can only be conjectured (MacDougal, 1925).

VARIATIONS IN THE SENSITIVITY OF MITOCHONDRIA TO CHANGE

One of the most puzzling properties of mitochondria is the ease with which those in gland cells are modified in pathologic conditions as compared with the resistance of apparently similar mitochondria in nerve cells. Examples of the sensitivity of mitochondria in gland cells have been mentioned. In nerve cells they are not noticeably influenced by extreme fatigue. Strongman (1917), and McCann (1918) found that in experimental poliomyelitis the mitochondria retain their usual filamentous shape, even in nerve cells which have undergone partial chromatolysis of their Nissl bodies. Moreover, Marinesco and Tupa (1922), as a result of their experiments on the effect of the tearing out of axons, have stated their conviction that the mitochondria are one of the most resistant formations in the cell. On the other hand, recent work (Ma, 1925) has shown that they are not so unmodifiable in beriberi as was formerly supposed (Clark, 1914).

INTERPRETATION OF MITOCHONDRIAL ALTERATIONS [5]

The fact that mitochondria are so widely distributed in forms ranging from the protozoa to man, and from the algae and fungi to the higher plants, has given rise to the belief that they serve some generalized function, such as protoplasmic respiration.[6] This is strengthened by the fact that they are also to be found in embryonic cells before the noticeable development of specialized activities, like secretion in gland cells and contractility in muscle cells. It must be remembered that the mitochondria are not all alike, but differ in their constitution, as already mentioned, within certain limits—an important point, first emphasized by Regaud. This investigator is responsible for the theory that the mitochondria act as plastids, choosing and selecting substances from the cytoplasm, condensing them in their interior, and changing them into diverse products. A conception of this kind is in harmony with many of the phenomena observed.

It seems to have been proved beyond question that in certain plants the mitochondria do serve as foci for the development of various substances of which it will suffice to mention chlorophyll and starch. Both of these materials are elaborated or concentrated within the interior of mitochondrial rods and filaments, where they can readily be recognized in living cells, even without the aid of supravital stains.[7] There is much to be said in support of the view that in animal cells the mitochondria, which are indistinguishable from those of plants (N. H. Cowdry, 1917), are also plastid-like in their activities. In all probability the mitochondria serve many functions both in different types of cells and in the same cells in different stages of cytomorphosis.

If we formulate our knowledge of mitochondria rather differently than is customarily done (Cowdry, 1926), it may perhaps be brought into line with recent studies in biochemistry, in which great emphasis is placed on the physical forces acting at surfaces of separation between fluids of different character and density. Certainly one of the most fundamental features of cellular architecture is the presence of innumerable mitochondria which, in the aggregate, afford a surface far greater in extent than that of the nuclear or plasma membranes. While fibrils, secretion antecedants and almost all other known products of cellular differentiation (with the possible exception of the Golgi apparatus) are but short-lived, and even the nuclear membrane is periodically lost

5. That mitochondria are merely symbiotic bacteria has often been suggested on the basis of insufficient evidence (Wallin, 1925, and earlier papers; also for criticism of this view, Cowdry and Olitsky, 1922, Meyer, 1925).

6. For further data, see Kingsbury (1912), Mayer, Rathery and Schaeffer (1914), and Cowdry (1918).

7. A critical analysis of the evidence presented is given by Noël and Mangenot (1925). For the catalytic action of mitochondria, see Emberger (1925).

and reconstituted, the mitochondria-cytoplasmic film is inseparable from phenomena which we call vital. That there is a close topographic association in the cell between this film and chemical changes of great variety has been proved. Enough has been said to show that the mitochondria-cytoplasmic film constitutes the most delicate indicator available of cellular injury, to which it responds by changes in shape, in extent, and by alterations in position.[8]

SUMMARY

To estimate even tentatively the value of the observations which have been made on mitochondria in pathologic conditions is difficult. Certainly no two cytologists would do so in the same terms: it would depend entirely on their points of view. We cannot look to any special disease and say that our knowledge of its character has been obtained by mitochondrial study, or that therapeutic measures for its alleviation have been greatly modified thereby. But we are in a position to make more thorough cytologic analyses of cellular lesions than heretofore. Indeed, the study of mitochondria has already been fruitful, because it has revealed the existence of early reactions of cells to injuries, no traces of which could have been detected by the older methods of technic. These early modifications have been observed chiefly in gland cells. Where, on the other hand, specialization has been carried to an extreme, as in neurology and hematology, comparatively little has been found out about the mitochondria.

In gland cells it has been shown that they are the first elements to change in cloudy swelling, and that they do so in the kidney and other organs under the influence of general anesthesia (Smith and Rettie, 1925). It has been found that they are the source of much if not all of the intracellular fat which appears as a result of phosphorus poisoning, and that they give rise to the lipoid droplets frequently reported in nerve cells. They are also concerned in the formation of lipochrome pigments. In regenerating cells and in some tumor cells they are greatly increased in number. In the thyroid Goetsch (1916) has been successful in correlating the clinical symptoms of hyperthyroidism with a marked increased in the number of mitochondria, and Bolt (1924) has confirmed and extended his findings. Both express the opinion that in thyroid

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8. According to a recent suggestion, the mitochondria can be interpreted "as representing the equilibrium of the cell with respect to lipin content. That is, the lipin which enters the cytoplasmic emulsion becomes combined with protein. If the transformation of protein-lipin material is not equal to its formation, an accumulation of the compound will occur, and after a certain accumulation has occurred, that is, when the cytoplasm has become saturated, it becomes precipitated out as mitochondria. This degree of saturation with lipin material is evidently typical of the cytoplasmic system." (Guthrie, M. J.: Ztschr. f. Zellf. u. Mikr. Anat. **2**:369, 1925.)

disease the study of mitochondria brings to light a condition of the secreting cells which would be overlooked in ordinary preparations. Seecof (1925) also has found that "The number, morphology, and distribution of the mitochondria in the thyroid cell vary directly with the degree of active hyperplasia or involution." With the mitochondria as indicators, Homans (1915) has associated diabetes in the dog with lesions in the B cells of the islets of Langerhans. In the liver Noël (1923) has correlated mitochondrial changes with the response to different dietary conditions. Other instances of a relation between alterations in the mitochondria and disturbances in cellular activity might be cited.

While our knowledge is so hazy regarding the rôle of mitochondria in normal physiologic processes, the significance of these alterations is doubtful; but as soon as we learn more about them, the information already secured, which seems often to be meaningless and even contradictory, may prove of real value. However this may be, their study in pathologic states is not in any sense premature. To halt investigations anywhere along the line would be unwise. If we restrict our researches to known cellular components, cytology will come to a standstill, because the function of the cell membrane itself is obscure. At the same time, investigators appreciating the complexity of vital phenomena and faced by the necessity of securing results will begin, perhaps rightly, with the relatively simple and will hesitate to devote their time and energies to the solution of the mitochondrial problem, which is so difficult of experimental analysis. It is a tenet of the mechanistic school that all natural phenomena will find their explanation in terms of physics and chemistry; but it may be many years before these sciences are sufficiently advanced to allow us to penetrate effectively much beneath the cell membrane.

However, our empirical knowledge of the mitochondrial constituents of protoplasm is so extensive and diversified that some discerning mind, fortified by an unexpected clue, may soon be able to put together the whole patchwork puzzle and arrive at an approximation to the truth which will serve as a working basis. This clue may very well come from observations on the behavior of mitochondria in unusual, or pathologic, conditions.

BIBLIOGRAPHY

D'Agata, G.: Sulla genesi del grasso e sulle modificazioni dell' apparato mitochondriale nell' intossicazione difterica, Internat. Monatsschr. f. Anat. u. Phys. **29**:443, 1913.

Alagna, G.: Sulla presenza di formazioni mitocondriali negli elementi costitutivi delle tonsille palatine normali, ipertrofiche e delle vegetazioni adenoidi, Arch. f. Zellforsch. **7**:27-40, 1911.

Anitschkow, N.: Zur Frage der trophigen Entmischung, Verhandl d. deutsch. path. Gesellsch. **17**:103-109, 1914.

Ueber Quellungs- und Schrumpfungserscheinungen an Chondriosomen, Arch. f. mikr. Anat. **97**:1-15, 1923.

Arnold, G.: On the Condition of Epidermal Fibrils in Epithelioma, Quart. J. Micr. Sc. **57**:283-299, 1912.

Bang, I., and Sjovall, E.: Studien über Chondriosomen unter normalen und pathologischen Bedingungen, Beitr. z. path. Anat. u. z. allg. Path., **62**:1-70, 1916.

Barratt, J. O. W.: Changes in Chondriosomes Occurring in Pathological Conditions, Quart. J. Micr. Sc. **58**:553-566, 1913.

Beckton, H.: On the Absence of Altmann's Granules from Cells of Malignant New Growths, Brit. M. J. **2**:859-861, 1909 a.

On Granules in Cells of Normal Tissues and New Growths, Arch. of Middlesex Hosp. **15**:182-191, 1909 b.

Altmann's Granules in Embryonic Tissues, ibid. **19**:103-110, 1910 a.

Altmann's Granules in Reference to Mouse Tumors, ibid. **19**:111-114, 1910 b.

On Granules in Cells of Normal Tissues and New Growths (Second Communication), ibid. **19**:115-126, 1910 c.

Beckton, H., and Russ, S.: The Effect of Radium Emanation on Altmann's Granules, Arch. Middlesex Hosp. **23**:99-105, 1911.

Benda, C.: Weitere Mitteilungen über die Mitochondria, Verhandl. d. Physiol. Gesellsch., 1899, pp. 376-383.

Bensley, R. R.: On the So-Called Altmann Granules in Normal and Pathological Tissues, Tr. Chicago Path. Soc. **8**:78, 1910.

Biondi, G.: Ueber Fettphanerosis in der Nervenzelle, Virchows Arch. f. path. Anat. **220**:222, 1915.

Bolt, W.: Mitochondria Content of the Thyroid as an Index of the Activity of the Gland, Jour. Lab. & Clin. Med. **9**:630-633, 1924.

Busacca, A.: Sulle modificazione dei plastosomi, etc., Rich. n. Lab. di Anat. norm. d. r. Univ. di Roma **18**:217, 1915.

Champy, C.: IV. Le rein, Arch. de Zool. exper. et gén. **55**:61-79, 1914.

Ciaccio, C.: Zur Physiopathologie der Zelle, Zentralbl. f. allg. Path. u. path. Anat. **24**:721, 1913.

Ciaccio, C., and Scaglione, S.: Beitrag zur cellulären Physiopathologie der Plexus chorioidei, Ziegler's Beitr. **55**:131-167, 1913.

Clark, E.: Regeneration of Medullated Nerves, J. Comp. Neurol. **24**:61, 1914.

Collin, R.: Sur les mitochondries extraneuronales dans l'écorce cérébrale irritée, Compt. rend. Soc. de biol. **67**:591-593, 1914.

Coltenot, Mulon, and Zimmern: Action des rayons x sur la corticale surrénale, Compt. rend. Soc. de biol. **73**:717, 1912.

Cowdry, E. V.: The Mitochondrial Constituents of Protoplasm, Contrib. Embryol., Carnegie Inst., Wash. **8**:39-160, 1918.

Conservatism in Cytological Nomenclature, Anat. Rec. **22**:239-250, 1921.

The Supravital Staining of Vaccine Bodies, J. Exper. Med. **36**:667-684, 1922.

Cytological Constituents, "General Cytology," Univ. of Chicago Press, 1924, pp. 311-382.

Studies on Etiology of Jagziekte II, J. Exper. Med. **43**:335-345, 1925.

Surface Film Theory of the Function of Mitochondria, Am. Naturalist, 1926.

Cowdry, E. V., and Nicholson, F. M.: Inclusion Bodies in Experimental Herpetic Infections of Rabbits, J. Exper. Med. **38**:695, 1923.

Cowdry, E. V., and Olitsky, Peter K.: Differences between Mitochondria and Bacteria, J. Exper. Med. **36**:521, 1922.

Cowdry, N. H.: A Comparison of Mitochondria in Plant and Animal Cells, Biol. Bull. **33**:196-228, 1917.

Cunningham, R. S.: Sabin, F. R., and Doan, C. A.: The Development of Leucocytes, Lymphocytes, and Monocytes from a Specific Stem-Cell in Adult Tissues, Contrib. Embryol., Carnegie Inst., Wash. **84**:227-276, 1925.

Da Fano, C.: On Golgi's Apparatus of Transplantable Tumor Cells, Seventh Rep. Imp. Cancer Res. Fund, 1921, pp. 66-91.

De Giacomo, A.: Sull' ipertrofia compensatoria e sui fenomeni cellulari nei reni dopo la ligatura di un uretere, Internat. Monatsschr. f. Anat. u. Physiol. **28**:208-232, 1911.

Dibbert, W.: Genese der Epithelveränderungen in der Niere bei experimenteller Diphtherie, ein Beitrag zur Pathologie der Zelle, Verhandl d. deutsch. path. Gesellsch. **17**:114, 1914.

Dominici, M.: Sulle formazioni mitochondriale e sui granuli di secrezione nelle prostata del cane e prostata umana ipertrofica, Folia urolog. **7**:295, 1913.

Dubreuil, G.: Le chondriome et le dispositif de l'activité sécrétoire, etc., Arch. d'Anat. Micr. **11**:53-151, 1913.

Duesberg, J.: Plastosomen, "Apparato reticolare interno," und Chromidialapparat, Ergebn. d. Anat. u. Entwcklngsgesch. **20**:567-916, 1912.

Emberger, L.: Les mitochondries sont-elles des catalyseurs, Bull. d'Hist. appl. **2**:369-374, 1925.

Emge, L. A.: A Cytological Study of the Kidney Cell in Long Continued Hyperfunction with Relation to Hypertrophy and the Mitochondrial Apparatus, Stanford Univ. Pub. Med. Sc. **1**:107, 1921.

Enderlin: Beitrag zur Nierenchirurgie, experimentelle und klinische Beobachtungen zur Histologie der nach Nephrektomiezurückbleibenden Niere, Deutsch. Ztschr. f. Chir. **41**:208-219, 1895.

Fahr: Zur Frage der sogenannten hyalin tropfigen Zelldegeneration, Verhandl d. deutsch. path. Gesellsch. **17**:119, 1914.

Favre, M., and Regaud, C.: Les mitochondries des cellules néoplasiques dans le carcinome de la mamelle chez la femme, Compt. rend. Soc. de biol. **71**:658, 1911.

Sur les mitochondries dans les cellules des sarcomes, ibid. **74**: 608, 1913 a.

Sur les formations mitochondriales dans les cellules néoplastiques des epiteliomes de la peau et des muqueuses dermopapillaires, ibid. **74**:688, 1913 b.

Fiessinger, N.: Contribution à l'étude des dégénérescences de la cellule hépatique au cours des intoxications brutales chez les batraciens, Compt. rend. Soc. de biol. **66**:494-496, 1909.

Giroud, A.: Réactions des substances albuminoïdes sur les chondriosomes, Compt. rend. Soc. de biol. **93**:158-160, 1925.

Goetsch, E.: Functional Significance of Mitochondria in Toxic Thyroid Adenomata, Bull. Johns Hopkins Hosp. **27**:129, 1916.

Goodpasture, E. W.: A Study of Rabies with Reference to a Neural Transmission of the Virus in Rabbits and the Structure and Significance of the Negri Bodies, Am. J. Path. **1**:547-582, 1925.

Grynfeltt, E.: Les plexus choroïdes chez les blessés de guerre, Montpel. méd. **40**:209, 1918.

Grynfeltt, E., and Euzière, J.: Recherches sur les variations fonctionnelles du chondriome des cellules des plexus choroïdes chez quelques mammifères, Compt. rend. de l'Ass. d. anat. **15**:197-205, 1913.

Recherches expérimentales sur les phénomenès cytologiques de la sécrétion du liquide cérébro-spinal, Compt. rend. Soc. de biol. **82**:1276-1278, 1919.

Grynfeltt, E., and Forgue, M.: Adenomyome intrapelvien de l'espace pararectal, Ass. franc. d. l'étude d. Cancer, 1922, p. 11.

Grynfeltt, E., and Lafont, R.: Sur la porphyrinurie expérimentale. Lésion de la cellule hépatique au cours de l'intoxication aiguë par le sulfonal, Montpel. méd. **43**:495, 1921 a.

Sur les modifications de la rate chez le lapin au cours de la porphyrinurie expérimentale par le sulfonal, ibid. **43**:502, 1921 b.

Lésion du foie chez un lapin porphyrinurique après intoxication chronique par le sulfonal, Compt. rend. Soc. de biol. **85**:292-293, 1921 c.

Signification physiopathologique de la margination des chondriosomes de la cellule hépatique au cours de l'intoxication par le sulfonal, ibid. **85**:406-408, 1921 d.

Sur la porphyrinurie expérimentale. Lésions du rein au cours de l'intoxication par le sulfonal chez le lapin, Compt. rend. Acad. d. sc. **173**:257-260, 1921 e.

Guilliermond, A.: Observations vitales sur le chondriome des végétaux, Rev. gén. bot. **31**:372-413, 446-508, 532-603, 635-770, 1919.

Hirsch, C.: Experimentell-anatomische Untersuchungen an der Nierenzelle, Anat. Hefte **41**: 131-172, 1910.

Hjelt, K. J.: Ueber die Mitochondria in den Epithelzellen der gewunden Nierenkanälchen bei der Einwirkung einiger Diuretika (Kaffein und Theocin), Virchows Arch. f. path. Anat. **207**:297-313, 1912.

Homans, J.: Degeneration of the Islands of Langerhans Associated with Experimental Diabetes in the Cat, J. Med. Res. **30**:49-68, 1914.

A Study of Experimental Diabetes in the Canine and Its Relation to Human Diabetes, ibid. **33**:1-51, 1915.

Israel, O.: Die anämische Nekrose der Nieren epithelien, Virchows Arch. f. path. Anat. **123**:310-334, 1891.

Jessen, J.: Om den mitochondriale Degeneration, Hospitalstid. **68**:82-88, 1925; J. A. M. A. **84**:932, 1925.

Key, J. A.: Secretory Phenomena in Pathological Human Thyroids, Anat. Rec. **23**:23, 1922.

Kingsbury, B. F.: Cytoplasmic Fixation, Anat. Rec. **6**:39-52, 1912.

Klein, S.: Ueber die sog. Schriddeschen Granula, Folia haemat. **9**:406-410, 1910 a.

Ueber die grossen einkernigen leukozyten des Leukämieblutes, ibid. **10**:475-516, 1910 b.

Kropp, B., and May, R. M.: A Study of Mitochondria in White Blood Cells Following Gaseous Inhalation, Anat. Rec. **27**:289-292, 1924.

Landsteiner, K.: Ueber trübe Schwellung, Ziegler's Beitr. **33**:237-280, 1903.

Lewis, W. H., and Lewis, M. R.: Behavior of Cells in Tissue Cultures, General Cytology, Univ. of Chicago Press, 383-448, 1924.

Lubarsch, O.: Fettdegeneration und Fettinfiltration, Ergebn. d. allg. Pathol. u. path. Anat. **3**:631-651, 1897.

Ludford, R. J.: The Distribution of the Cytoplasmic Organs in Transplantable Tumor Cells, with Special Reference to Dictyokinesis, Proc. Roy. Soc. B. **97**:50, 1924 a.

Cell Organs During Keratinization in Normal and Malignant Growth, Quart. J. Micr. Sc. **69**:27, 1924 b.

The General and Experimental Cytology of Cancer, J. Roy. Micr. Soc. **272**:249-292, 1925 a.

The Cytology of Tar Tumors, Proc. Roy. Soc. **98**: (B) 557-577, 1925 b.

Luna, E.: Sulle modificazioni dei plastosomi delle cellule nervose nel trapianto ed in seguito al taglio dei nervi, Anat. Anz. **44**:413-415, 1913.

Ma, W. C.: Preparations of the Pancreas of the Guinea-Pig to Show Changes in Mitochondria Due to Inanition and Re-Feeding, Anat. Rec. **25**:157, 1923.

Changes in the Pancreatic Cell of the Guinea-Pig During Inanition and Refeeding, ibid. **27**:47-60, 1924.

A Study of the Mitochondrial Elements of Spinal Ganglion Cells of Beriberi Fowls, Am. J. Anat. **36**:215-234, 1925.

MacDougal, D. T.: Accretion and Distention in Plant Cells, Am. Naturalist. **59**:336, 1925.

Mangenot, G.: Recherches sur les constituants morphologiques du cytoplasma des Algues, Arch. de Morph. gén. et expér. **9**:1-340, 1921.

Marinesco, G., and Tupa, A.: Recherches histo-pathologiques sur les mitochondries, Compt. rend. Soc. de biol. **87**:292-296, 1922.

Mayer, A., and Rathery, F.: Modifications histologiques du rein normal au cours des diurèses provoquées, Compt. rend. Soc. de biol. **62**:738-740, 776-777, 1907.

Modifications histologiques du rein normal au cours des diurèses provoquées. 3. Etudes sur le lapin, ibid. **63**:108-110, 1907.

Mayer, A.; Rathery, F., and Schaeffer: Les granulations ou mitochondries, etc. J. de Physiol. et de Path. gén. **16**:607-622, 1914.

McCann, G. F.: A Study of Mitochondria in Experimental Poliomyelitis, J. Exper. Med. **27**:31-36, 1918.

Meyer, K. F.: "Bacterial Symbioses," J. Infect. Dis. **36**:1-107, 1925.

Miller, S. P.: Effects of Various Types of Inanition upon the Mitochondria in the Gastrointestinal Epithelium and in the Pancreas of the Albino Rat, Anat. Rec. **23**:205-210, 1922.

Mira, M. F.: Sur l'état des capsules surrénales chez les animaux ovariectomisés, Bull. Soc. Portugaise Sc. Nat. **6**:34-46, 1912.

Mislawsky, N.: Ueber das Chondriom der Pankreaszelien, Arch. f. Mikr. Anat. **81**:394-429, 1913.

Murray, J. A.: A Transplantable Sarcoma of the Guinea-Pig, J. Path. & Bacteriol. **20**:260-268, 1906.

Nageotte, J.: L'organisation de la Matière dans ses rapports avec la vie, Paris, Librairie Felix Alcan, 1922.

Nicholson, F. M.: A Cytological Study of the Nature of Rickettsia in Rocky Mountain Spotted Fever, J. Exper. Med. **37**:221-230, 1923 a.

Changes in the Mitochondria Produced Experimentally in the Thyroid Gland, ibid. **39**:63-75, 1923 b.

Noël, R.: Recherches histophysiologiques sur la cellule hépatique des mammifères, Arch. d'Anat. Micr. **19**:1-158, 1923.

Noël, R., and Mangenot, G.: Les fonctions élaboratrices du chondriome. Etat actuel de la question, Bull. d'Hist. appl. **2**:302-316, 1925.

Noël, R., and Rosier, M.: Chondriome of Hepatic Cells in Experimental Precirrhosis, Compt. rend. Soc. de biol. **90**:1436-1438, 1924.

Okuneff, N.: Studien über Zellveränderungen im Hungerzustande (Das Chondriom), Arch. f. mikr. Anat. **97**:187-203 1923.

Oliver, J.: A Further Study of the Regenerated Epithelium in Chronic Uranium Nephritis, J. Exper. Med. **23**:301-322, 1916.

Ono, Shun Ichi: Effect of Starvation and Refeeding, Proc. Anat. & Anth. Ass. of China, China Med. J., Anat. Suppl., 1920.

Ophüls, W.: Altmann's Granules in Granular and Fatty Degeneration in the Kidney, Proc. Soc. Exper. Biol. & Med. **4**:135-137, 1907.

Pizzini, B.: Ueber die Secretionserscheinungen in der Nierenzelle bei der Diurese, Internat. Monatsschr. f. Anat. u. Phys. **25**:108-148, 1908.

Policard, A.: Contribution a l'étude du mécanism, etc., Arch. d'anat. micr. **12**:177-288, 1910.

Policard, A., and Garnier, M.: Altérations cadavériques des épithéliums rénaux, Compt. rend. Soc. de biol. **59**:678-680, 1905.

Des lésions rénales provoquées par l'injection sous-cutanée de doses massives de Phlorhizine, ibid. **62**:834-836, 1907.

Porcelli-Titone, F.: Der Mitochondrienapparat der Geschwulstzellen, Beitr. z. path. Anat. u. z. allg. Path. **58**:237-249, 1914,

Pringosen, R. E.: Histological Studies of Tumor Cells after X-Ray. I, Proc. N. Y. Path. Soc. **22**:175-178, 1922.

Rasmussen, A. T.: The Mitochondria in Nerve Cells during Hibernation and Inanition in the Woodchuck (Marmota monax), J. Comp. Neurol. **31**:37-49, 1919.

The Hypophysis Cerebri of the Woodchuck (Marmota monax) with Special Reference to Hibernation and Inanition, Endocrinol. **5**:33-66, 1921.

Regaud, C., and Favre, M.: Nouvelles recherches sur les formations mitochondriales de l'épiderme humain, à l'état normal et pathologique, Compt. rend. Soc. de biol., **72**:328-331, 1912.

Rio Hortega, P. del: Contribución al estudio de la fina textura de las células cancerosas, Trab. d. Lab. d. Invest. biol. Univ. Madrid **12**:85-96, 1914.

Romeis, B.: Beobachtungen über Degenerationserscheinungen von Chondriosomen, Arch. f. mikr. Anat. **80**:129-170, 1912.

Das Verhalten der Plastosomen bei der Regeneration, Anat. Anz. **45**:1-19, 1913.

Ruggeri, E.: Modificazioni del contenuto lipomitocondriale delle cellule della pineale dopo ablazioni complete degli organi genitali, Riv. di patol. nerv. **19**:649-659, 1914.

Russo, A.: Sui mutamenti che subiscono i mitochondri ed i materiali deutoplas mici dell' oocite di Coniglia in diversi periodi di inanizione, Arch. f. Zellf. **5**:173-181, 1910.

Sabin, F. R.; Austrian, C. R.; Cunningham, R. S., and Doan, C. A.: Studies on the Maturation of Myeloblasts into Myelocytes and on Amitotic Cell Division in the Peripheral Blood in Subacute Myeloblastic Leucemia, J. Exper. Med. **40**:845-871, 1924.

Sappington, C. O.: Mitochondria in Red Corpuscles in Experimental Anaemia. Arch. Int. Med. **21**:695-704, 1918.

Schilling, C.: Das Verhalten der Altmann's schen Granula bei der trüben Schwellung, Virchows Arch. f. path. Anat. **135**:470-479, 1894.

Scott, J. T.: Effect of Different Hydrogen Ion Concentrations on Mitochondria in the Liver Cell, Anat. Rec. **29**:396, 1925.

Scott, W. J. M.: Experimental Mitochondrial Changes in the Pancreas in Phosphorus Poisoning, Am. J. Anat. **20**:237-253, 1916.

Seecof, D. P.: Studies on Mitochondria. I. The Changes Occurring during Experimental Thyroid Hyperplasia and Its Involution with Iodine, Am. J. Path. **1**: 295, 1925.

Shipley, P. G.: The Mitochondrial Substance in the Erythrocytes of the Embryo Pig, Folia haemat. **20**:61-86, 1915.

Sjöbring, N.: Ueber das Formol als Fixierungsflüssigkeit, Anat. Anz. **17**:273-304, 1900.

Smith, Lorrain, J., and Rettie, Theodore: The Early Phases of Cell Injury with Special Reference to Mitochondria, J. Path. & Bacteriol. **28**:627-632, 1925.

Sokoloff, B.: Mitochondries de la cellule maligne, Bull. Inst. Sc., Petrograd, Compt. rend. Soc. de biol. **87**:1202-1204, 1922.

Strongman, B. T.: A Preliminary Experimental Study on the Relation Between Mitochondria and Discharge of Nervous Activity, Anat. Rec. **12**:167-171, 1917.

Suzuki, T.: Zur Morphologie der Nierensekretion unter physiologischen und Pathologischen Bedingungen, Jena, 1912.

Takaki, K.: Ueber die Stäbchenstrukturen der Niere, Arch. f. mikr. Anat. **70**: 245-265, 1907.

Thurlow, M. DeG.: Observations on the Mitochondrial Content, etc., Anat. Rec. **10**:253, 1916.

Quantitative Studies on Mitochondria in Nerve Cells, Contrib. Embryol., Carnegie Inst., Washington **6**:35-44, 1917.

Torraca, L.: Il comportamento dei condriosomi nella rigenerazione de muscoli striati, Arch. f. Zellforsch. **12**:539-552, 1914 a.

Alcune osservazioni sui condriosomi delle cellule cartilaginée nell coda del tritone rigenerante, Anat. Anz. **45**:459-474, 1914 b.

Alcune osservazioni sulla rigenerazione e sul processo di secrezione delle glandole velogene delle Triton cristatus, Arch. ital. di. anat. e di embriol. **15**: 283-330, 1916.

Veratti, E.: Sulla fine struttura delle cellule di alcuni tumori, Boll. Soc. med. chir. di Pavia **23**:34-45, 1909.

Wakefield, H.: Preparations of Pancreas of Guinea-Pig to Show Changes in Mitochondria Produced by Vitamin Deficiency, Anat. Rec. **25**:158, 1923.

Wallin, I. E.: On the Nature of Mitochondria. IX. Demonstration of the Bacterial Nature of Mitochondria, Am. J. Anat. **36**:131-150, 1925.

Weed, L. H.: The Effects of Hypotonic Solutions upon the Cell. Morphology of the Choroid Plexuses and Central Nervous System, Am. J. Anat. **32**:253-276, 1923.

Wilson, E. B.: Protoplasmic Systems and Genetic Continuity, Am. Naturalist **59**:481, 1925.

Wood, F. C., and Hartman, A.: Mitochondria in Tumors, Proc. N. Y. Path. Soc. **22**:173-174, 1922.

Correspondence

January 23, 1926.

To the Editor:—In a review, "Relation of Atopic Hypersensitiveness (Hay-Fever, Asthma) to Anaphylaxis," by A. F. Coca (ARCH. PATH. **1**:96 [Jan.] 1926) two references are made to the work of Karsner and Ecker, one misleading and the other untrue. In a discussion of the term "desensitization," page 100, Coca refers to the discussion of "nonspecific desensitization" by Karsner and Ecker in 1922, but fails to mention the fact that the title of the paper refers to the "desensitized state." At that time there had been little criticism of the inexactitude of the term in general and none of its usage in reference to nonspecific agents. Furthermore, Coca is either unfamiliar with or has withheld mention of a subsequent paper by the same authors (*J. Infect. Dis.* **34**:636 [June] 1924) in which they recognize the objections presented, and therefore employ the term "inhibition."

In discussing the term "allergy," Coca states, on page 102, that "Karsner and Ecker do not mention the word" in their book "The Principles of Immunology." A book should not be quoted or misquoted by reference solely to the index. On page 209 of this book, published in 1921, reference is made to the work of Pirquet and Schick in the paragraph introducing the subject of anaphylaxis. The word allergy is not only "mentioned," but the authors state that "the usage of the term at the present time is confusing and definitions vary; we, therefore, prefer not to employ it." Had Coca been more careful in his quotation, he might have been interested to see how closely this statement made in 1921 agrees with his own of 1926, in which he says (p. 102), "in view of this complete want of agreement as to the meaning of the term, it must be looked upon as lacking scientific standing as well as any practical usefulness,"

Justice to our work, if not to ourselves, dictates the writing of this letter. Its brevity is in keeping with a desire to adhere strictly to the matter in hand and to avoid polemics that might arise from more extended discussion of the points at issue.

HOWARD T. KARSNER, M.D., and
E. E. ECKER, PH.D., Cleveland.

To the Editor:—I regret having to admit the justness of the foregoing criticism by Karsner and Ecker, and I am pleased to find myself in essential agreement with these authors on the two points in question.

ARTHUR F. COCA, M.D., Cleveland.

Notes and News

Dr. Noguchi Receives Degree.—Dr. Hideyo Noguchi received the degree of Doctor, Honoris Causa, Nov. 28, 1925, at the Sorbonne, Paris.

Election of Bass.—Dr. C. C. Bass, dean and professor of experimental medicine in the Tulane University Medical School, was elected president of the Southern Medical Association on Nov. 12, 1925.

Wherry Appointed to Health Board.—Dr. William B. Wherry, professor of bacteriology at the University of Cincinnati, has been appointed a member of the Cincinnati Board of Health to succeed the late Dr. Edward Walker.

Hagan to Study in Europe.—W. A. Hagan, professor of veterinary pathology and parasitology at Cornell University, has been granted a leave of absence for the purpose of studying in Europe under a fellowship from the International Education Board.

Woman's Medical College.—Dr. Helen Ingleby, demonstrator of pathology at St. George's Hospital, London, England, is acting as professor of pathology at the Woman's Medical College of Pennsylvania, in place of Dr. Maude Abbott, who has returned to McGill University, Montreal.

Rosenow Receives Callahan Memorial Medal.—The Callahan Memorial Medal of the Ohio State Dental Society was awarded to Dr. E. C. Rosenow of the Mayo Foundation, Dec. 2, 1925, for his work on focal infection and elective localization. Last June Dr. Rosenow received the degree of LL.D. from Park College, Parkville, Mo.

Berglund Elected Professor of Medicine.—The University of Minnesota has appointed Dr. Hilding Berglund, a native of Sweden, as professor and head of the department of medicine to succeed Dr. S. Marx White, who will devote his full time to private practice. Dr. Berglund came to this country in 1920 to study under Dr. Folin at Harvard University, and since 1923 has been assistant professor of medicine in Harvard University Medical School and an associate in medicine at the Peter Bent Brigham Hospital, Boston.

Faculty Appointments at Tulane.—Henry Laurens of Yale University has been appointed professor of physiology in Tulane University to fill the vacancy created by the resignation of Walter Garrey to accept the professorship of physiology in Vanderbilt University, Nashville, Tenn.

The Society for Experimental Biology and Medicine has established a branch at Tulane University, to be known as the Southern Branch. The first officers are: Charles W. Duval, chairman; John H. Musser, vice chairman; Irving Hardesty, secretary.

Hansmann Appointed.—Dr. G. H. Hansmann has been appointed acting head of the department of pathology and bacteriology in the University of Iowa in the place of F. W. Mulsow who resigned to take up hospital and private work in Cedar Rapids, Iowa. Dr. Hansmann graduated in medicine from the University of Iowa in 1918, served as hospital chemist and clinical assistant in his alma mater for three years and as resident pathologist in the Peter Bent Brigham Hospital and instructor in pathology in Harvard Medical School in 1922-1923, returning to the University of Iowa in 1924 as hospital pathologist.

Viennese Professor at Mt. Sinai.—Dr. Ernst Pribram, professor of experimental medicine in the University of Vienna, on leave of absence for one year, is acting as pathologist to Mount Sinai Hospital in Milwaukee.

Albritton to Chulalongkorn University.—It is reported that Errett C. Elbritton, formerly fellow in medicine of the National Research Council, has accepted an offer of appointment as professor of physiology in Chulalongkorn University.

Appointments at Chicago.—At the University of Chicago, Dr. Nathaniel Kleitman has been appointed assistant professor of physiology, Dr. Paul R. Cannon assistant professor of pathology, and Dr. Charles Philip Miller has been made an assistant professor in medicine on the Douglas Smith Foundation to do research work abroad.

Blood Grouping of Filipinos.—Mrs. Ella T. Grove, instructor in immunology in Cornell University Medical College and assistant research immunologist in the New York Hospital, is making a study of the iso-agglutinative blood grouping of Philippine tribes under the auspices of the committee on problems of human migration of the division of psychology and anthropology of the National Research Council. On the way to the Philippines, Mrs. Grove visited the Ainus in Japan and made observations on the distribution of blood groups in that interesting race.

Death of Hewlett.—Albion Walter Hewlett, professor of medicine in Stanford University School of Medicine, San Francisco, died of brain tumor, Nov. 10, 1925, aged 51. Dr. Hewlett was secretary of the section on pathology and physiology of the Scientific Assembly of the American Medical Association, 1911-1912, and chairman 1912-1913, and his work as member of the Council on Pharmacy and Chemistry of the American Medical Association (1916-1922) was of great value. He was the author of "Functional Pathology of Internal Diseases."

American Type Culture Collection.—The Annual Report of Dr. L. A. Rogers, chairman of the committee in charge of the American Type Culture Collection, shows that the available cultures have increased from 175 to 722 during the period Feb. 1 to Dec. 15, 1925, including 69 molds and 122 yeasts. A total of 360 orders has been filled, involving the sending of 1,540 cultures to 240 persons and institutions. The committee has established a price of one dollar per culture, with addition for packing and postage. A temporary list of cultures is available. A printed catalog is planned for the near future. Communications should be sent to The American Type Culture Collection, John McCormick Institute for Infectious Diseases, 637 S. Wood Street, Chicago.

Uses of Bunion Pads as Shields After Vaccination.—Deaths from tetanus may result from the use of bunion pads for shields or dressings after vaccination, is the warning issued by the U. S. Public Health Service, Washington, D. C. Fatalities from this cause have recently been reported from various parts of the country. Not only may the fresh felt pad be contaminated with the lockjaw germs, but the covering of the inoculated spot by any kind of shield will tend to keep the place wet and warm and therefore make it a favorable culture ground for the growth of microbes, especially the tetanus bacteria. Loose, cool, gauze dressings do not harm if properly cared for, but the best dressing is none at all, in the opinion of the service, for the dry scab that naturally and quickly forms is sufficient protection in most cases, and if the skin has been properly sterilized in advance there is no fear of foreign infection.

DOCTORATES IN MEDICAL SCIENCES CONFERRED BY AMERICAN UNIVERSITIES, 1922-1923, 1923-1924, 1924-1925

Callie Hull and Clarence J. West, Research Information Service, National Research Council, Washington, D. C.

The following list of doctorates in Anatomy, Bacteriology, Pathology and Physiology granted during the years 1922-1925, has been compiled from information supplied through the courtesy of the various American universities granting the doctor's degree. It is offered as a suggestive guide to the research work which is being carried out at different universities and to the persons interested in special fields of investigation.

ANATOMY

1922-1923:

Chicago: Theodore Hieronymus Bast, "Maxillary Sinus of the Dog, with Special Reference to Certain New Structures, Probably Sensory in Nature." Daniel Bartlett MacCallum, "Arterial Blood Supply of the Macamalean Kidney." Mabel Bishop, "Nervous System of a Two-headed Pig Embryo."

Columbia: Ruth Rand Atterbury, "Development of the Metanephric Anlage of the Chick in Allantoic Crafts."

Cornell: Christianna Smith, "Origin and Development of the Carotid Body."

Kansas: Hervey S. Faris, "Nature, Origin and Significance of Pigment in Embryos of Amblystoma."

Minnesota: Halbert Louis Dunn, "Growth of the Cerebrum and Its Integral Parts." Shirley Putnam Miller, "Effects of Inanition upon the Stomach and Intestines of Albino Rats Underfed from Birth for Various Periods." Emily Helen Payne, "Omentum of the Rabbit, with Special Reference to Hematological Problems." Samuel Bernard Solhaug, "Study of the Developmental Topography of the Pelvic Organs of the Female Fetus."

1923-1924:

Chicago: Percival Allen Gray, Jr., "The Cortical Lamination Pattern of the Opossum, Didelphys virginiana." Jeannette Brown Obenchain, "The Brain of a South American Marsupial, Caenolestes."

Minnesota: Gustav Joseph Noback, "A Study of the Developmental Anatomy of the Respiratory System in Men."

Washington University, St. Louis: Mildred Trotter, "The Life Cycles of Hair in Selected Regions of the Body."

1924-1925:

Chicago: Patrick Arthur Delaney, "The Mesothelium of Turtles." Daniel Lytle Stormont, "Nerve Endings and Secretory Activity in the Submaxillary Gland of the Rabbit."

Cincinnati: B. Noland Carter, "The Diagnosis and Treatment of Fractures of the Skull Based upon a Study of 250 Cases."

Minnesota: Laurence Francis Richdorf, "A Quantitative Study of the Growth of the Normal Infant in the First Year."

BACTERIOLOGY

1922-1923:

Brown: John Edward Blair, "Contribution to the Study of the Twort-d'Herelle Phenomenon." Charles Arthur Stuart, "Effect of Environmental Changes on the Growth, Morphology, Physiology, and Immunological Characteristics of Bacterium typhosum."

Chicago: Sara Elizabeth Branham, "Toxic Products of Bacillus enteritidis. Production of Lung Hemorrhages and Associated Phenomena in Rabbits and Guinea-Pigs." Willis Eugene Gouwens, "Physico-Chemical Studies of Some Immunity Reactions: The Meiostagmin Reaction. Effect of Temperature on the Velocity of Reaction in Hemolysis. Acid Agglutination of the Paratyphoid Bacilli." Leland Wilbur Parr, "Intestinal Spirochetes." William Barnard Sharp, "Common Cold, an Etiologic Study." Harry Montgomery Weeter, "Infectious Abortion in Domestic Animals."

Columbia: Louis Freedman, "Nutrition Factors in the Growth of Certain Yeasts and Bacteria." Ann Gayler Kuttner, "Bacteriophage Phenomena." Strashimir A. Petroff, "Immunological Studies in Tuberculosis." John Winter Rice, "Studies on Streptococcus hemolyticus of Scarlatinal and Other Origins."

Cornell: Merl Perrott Moon, "Comparison of the Direct Microscopic and Agar Plate Methods for the Examination of Bacteria in Milk."

George Washington: Ella Morgan Austin Enlows, "Bacillary Dysentery with Special Reference to the Toxins Produced by the Causal Organisms and the Antitoxic Content of Antidysenteric Serums." Arnold Parker Sturtevant, "Development of American Foul-Brood in Relation to the Metabolism of Its Causative Organism."

Illinois: Paul William Allen, "Attenuation of Bacteria Due to Temperature Shock." Lethe Eleanora Morrison, "Studies on Thermophilic Bacteria."

Johns Hopkins: Clennie Elsie Bailey, "Study of the Normal Immune Hemagglutinins of the Domestic Fowl with Respect to Their Origin, Specificity, and Identity." Elery Ronald Becker, "Studies on Some Protozoan Flagellates Entozoic in the Alimentary Tracts of North American Insects." Lemmie Roscoe Cleveland, "Physiological and Symbiotic Relationships Between the Intestinal Protozoa of Termites and Their Host, with Special Reference to Reticulitermes flavipes Kollar." Rachel Emilie Hoffstadt, "Bacterial Analysis of Ground Beef with Special Reference to Sanitary Standards." Bertha Langwill, "Determination of the Character of Acids Produced by Hemolytic and Non-Hemolytic Streptococci from Pathogenic Sources and from Milk." Henrietta Lisk, "Study of the Decomposition Products of Spore-Bearing Bacteria in Heated Milk." Horace Mann Powell, "Biological Study of the Diphtheria Bacillus."

New York: Agnes Goldman, "Bacterial Microbes in the Intestines of Normal and Pathological Persons."

Wisconsin: Orvin Richard Brunkow, "Study of the Influence of Inoculation upon the Sauerkraut Fermentation." Alfred Larson, "Use of Ultraviolet Rays in the Production of Antigens."

Yale: John Joseph Enright, "Studies on the Wildbolz Auto-Urine Reaction." Isadore Sydney Falk, "Influences of Certain Electrolytes upon the Viability and the Chemical and Physical Properties of Bacteria." Walter Leroy Kulp, "Comparative Study of Lactobacillus acidophilus (Moro) and Lactobacillus bulgaricus (Massol.)." Luther Kyner Musselman, "Natural Immunity in the Newborn."

1923-1924:

Brown: Minot Joy Crowell, "Morphological and Physiological Variations in the Descendants of a Single Diphtheria Bacillus."

California: Carrie Castle Dozier, "A Biological Study of B. botulinus."

Chicago: Noel Paul Hudson, "The Inoculation of White Mice with Pfeiffer's Bacillus: Mixed Cultures." Robb Spalding Spray, "I. The Bacteria in Normal and Diseased Lungs of Swine. II. A Bacteriological Study of Pneumonias of Sheep. III. Notes on a Diplococcus Associated with Caseous Lymphadenitis and Pneumonia of Sheep." William Alfred Starin, "Studies on Botulism. (a) Isolation of Pure Cultures. (b) Agglutination Reaction of Clostridium botulinum. (c) Complement Binding Reaction of Clostridum botulinum."

Cornell: Morton Charles Kahn, "Pt. 1. A Cultural Study of Anaerobic Spore-Bearing Bacteria with Strains Isolated by the Barber Single Cell Technic. Pt. II. Anaerobic Spore-Bearing Bacteria of the Human Intestine in Health and Certain Diseases." Ernest Edgar Pittman, "The Bacterial Content of Creamery Wastes."

Kansas: Cornelia Mitchell Downs, "Antigenic and Metabolic Studies of Eberthelia typhi (Bacillus typhosus)."

Michigan: Malcolm Herman Soule, "Respiration of Trypanosoma lewisi and Leishmania tropica." George William Collins, "Studies on the Source of the Lytic Principle; and on the Origin of Transmissible Bacterial Autolysis."

Wisconsin: William Carroll Frazier, "The Rôle of Bacteria in Curdling Milk on Sterilization."

Yale: George James Hucker, "Studies on the Coccacea." James George McAlpine, "Bacteriological and Serological Studies on Infectious Abortion."

1924-1925:

Chicago: John Tennyson Myers, "The Relationship of Hard Water to Health."

Illinois: Luther Thompson, "Clostridium botulinum Growth and Toxin Production in Canned Foods."

Johns Hopkins: Eleanor Albert Bliss, "Anaerobic Spore-Bearing Bacteria in Baltimore Milk." Vladimir Triphon Dimitroff, "Spirochaetes and Spirilla in Baltimore Market Oysters." Martha Oliver Eckford, "A Study of Thermophiles in Baltimore Milk Supply." Calista Post Eliot, "A Study of the Bacteriology of Decomposing Oysters." William Anthony Feirer, "Studies on Some Obligate Thermophilic Bacteria from Soil." Martin Frobisher, Jr., "The Effect of Surface Tension on Bacteria."

Michigan: Max Skidmore Marshall, "Observations on d'Herelle's Bacteriophage."

Pennsylvania: Miriam Stewart, "The Influence of Inhaled Calcium Dust on Pulmonary Tubercular Infection."

Wisconsin: Helen-Louise Fulton, "The Fermentability of Various Cereals and Other Substances by Granulobacter pectinovorum and the Action on the Proteins of Such Materials." Maurice Mulvania, "Studies on the Nature of the Virus of Tobacco Mosaic." Jan Augusto Viljoen, "I. Effect of Wood Pulp Cellulose on Plant Growth. II. The Isolation and Fermentation Characteristics of a Thermophilic Cellulose Destroying Microorganism." William Harmon Wright, "The Nodule Bacteria of Soybeans."

Yale: Leon Alson Bradley, "The Decomposition of Cellulose by Aerobic Bacteria," Philip Edwards, "The Relation of Bacterium anatum to the Para B-Suipestifer Group of Bacteria." Elizabeth Helen Fleeson, "The Influence of Electrolytes upon the Electrophoresis of Certain Organisms." Helen Wheeler Ford, "A Statistical Study on Neonatal Mortality and Its Control, with Special Relation to the Factor of Mother Nativity." Newton Wheeler Larkum, "Bacteriophagy in Urinary Infection." Margaret Frances Upton, "The Electric Charge on Certain Species of Vegetable Organisms."

PATHOLOGY

1922-1923:

Chicago: Elizabeth Pauline Wolf, "Studies on the Chemical Principles of the Reaction of Inflammation."

Harvard: Ewald Tomanek, "Epidemiology of Pneumonia."

Johns Hopkins: Donald Leslie Augustine, "Studies on the Activities of the Infective Larvae of Necator Americanus." Shulamite Ben-Harel, "Studies on Bird Malaria in Relation to the Mechanism of Relapse." Mary Gover, "Statistical Study of the Etiology of Benign Hypertrophy of the Prostate Gland." Claire McDowell, "Effect of Different Temperatures and Relative Humidities on the Resistance of Rats to a Pneumococcus Infection." Florence King Payne, "Studies on the Activities of Infective Hookworm Larvae with Special Reference to Vertical Migration." Joseph Mehollin Scott, "Critical Study of the Reaction of the Rabbit Cornea to Inoculation with Variola and Varicella Material." Norman Rudolph Stoll, "Studies in Hookworm Disease Control Based on a Dilution Egg-Counting Technique."

Yale: Ettore Cimpolini, "Cocobolo Wood Poisoning." Margaret M. Justin, "Correlation of Weather and Mortality as Shown by the Mortality Statistics of New York City for the Years 1883-1888."

1923-1924:

Brown: Jane Frances Peckham, "Pathology and Immunity of Yeast."

California: William Walter Reich, "Studies on Trypanosoma brucei and Experimental Nagana."

Chicago: Louis Henry Braafladt, "The Effect of Kaolin on the Intestinal Flora in Normal and Pathological Conditions." Louis Leiter, "Experimental Chronic Glomerulonephritis." Bernard Portis, "The Rôle of the Omentum of Rabbits, Dogs and Guinea-Pigs in Antibody Production." Meta Louise Schroeder, "I. The Effect of Bacterial Infection upon Antibody Production. II.The Effect of Pneumococcus Extract upon Antibody Production." James Persons Simonds, "Leukemias, Pseudoleukemias, and Related Conditions in Mice." Louis Wendlin Sauer, "Studies in Hypertrophic Pyloric Stenosis."

Johns Hopkins: George Hugh Boyd, "The Influence of Experimental Factors upon the Course of Infection with Plasmodium Praecox, with Special Reference to Treatment." Frances Adele Coventry, "The Reaction Product Which Inhibits Reproduction of the Trypanosomes in Infections with Trypanosome lewisi, with Special Reference to Its Changes in Titer Throughout the Course of the Infection." William Thurber Fales, "A Quantitative Study of the Age Distributions of the Common Infectious Diseases of Childhood in the United States."

1924-1925:

Cornell: Charles Victor Noback, "A Study of Nephritis in Domestic Animals."

Johns Hopkins: Francis O. Holmes, "Herpetomonad Flagellates in Milk Weed in the United States." Elizabeth Ingersoll Parsons, "Studies in Complement Splitting with Special Reference to the Activation of Yeast Absorbed and Complement Deficient Guinea-Pig Serum." William Westbrook Redfern, "A Study of the Primary Toxicity of Heterophile Immune Rabbit Serum for Guinea-Pigs and Its Apparent Relation to the Phenomenon of Anaphylaxis." Lucy Graves Taliaferro, "Infection and Resistance in Bird Malaria, with Special Reference to Periodicity and Rate of Reproduction of the Parasite."

PHYSIOLOGY

1922-1923:

Chicago: Helen Bourquin, "Study on the Permeability of the Placenta." Carl Albert Dragstedt, "Studies in Intestinal Obstruction." Marie Dye, "Basal Metabolism of Normal Women and Its Relation to Creatine and Creatinine Elimination." Nathaniel Kleitman, "Studies on the Physiology of Sleep."

Cincinnati: John Emil Haldi, "Effects Produced on the Body Weight and the Various Internal Organs of the White Rat by Feeding the Desiccated Anterior Lobe of the Hypophysis."

Columbia: Joseph Tulgan, "Study of the Relations of Afferent Impulses to the Activity of the Central Cardio-Vascular Nervous Mechanism."

Cornell: Howard Scott Liddell, "Preliminary Study of the Learning and Activity of Sheep."

Harvard: Fred Reece Griffith, Jr., "Nervous and Hormone Control of the Blood Sugar."

Iowa University: Harry Matloch Hines, "Creatine Metabolism."

Minnesota: Hymen Shalit Lippman, "Blood in the Newborn Period."

New York: Ernest Frithiof Boström, "Studies on Factors Producing a Rapid Increase or Decrease in the Number of Red and White Cells in the Bloodstream."

Northwestern: Loyal Edward Davis, "Deep Sensibility of the Face."

Radcliffe: Annie Stone Minot, "Distribution of Lead in Acute and Chronic Lead Poisoning."

Wisconsin: Ko-Kuei Chen, "Experimental Atrophy of Muscle." Chauncey Depew Leake, "Factors Indicating Reduced Oxidation in Certain Blood Vascular Changes, with Special Reference to Morphine and Certain Types of Experimental Pneumonias." Ethel Ronzoni, "Acid-Base Equilibrium of the Blood in Exercise."

Yale: Alfred Chanutin, "Factors Involved in the Regulation of Blood Volume After Introduction of Fluids into the Body." Precioüs Mabel Nelson, "Rôle of Maternal Diet During Lactation in the Nutrition of the Young." Florence Barbara Seibert, "Febrile Reactions Following the Injection of Non-Specific Agents into Rabbits."

1923-1924:

Chicago: Theodore Elliott Boyd, "The Influence of Alkalies on the Secretion and Composition of Gastric Juice." Nelson Franklin Fisher, "Studies on the Pancreatic Hormone." Margarete Meta Hedwig Kunde, "The After Effects of Prolonged Fasting on the Basal Metabolic Rate."

Columbia: Frederick Bonner Flinn, "Some Effects of Various Environmental Temperatures upon the Blood of Dogs." Aleita Hopping, "Seasonal Changes in the Gases and Sugar of the Blood and the Nitrogen Distribution in the Blood and Urine of the Alligator." Cecil Dunmore Murray, "The Acid-Base Equilibrium in Simple Two-Phase Systems."

Cornell: Meyer Bodansky, "Experimental Studies on Liver Injury and on Anemia." Frank Anton Csonka, "On the Administration of Various Proteins with Benzoic Acid to a Pig."

Harvard: Raoul Michel May, "The Relation of Nerves to Degenerating and Regenerating Taste Buds."

Illinois: Jane Marie Leichsenring, "Factors Influencing the Rate of Oxygen Consumption in Unicellular Organisms."

Johns Hopkins: Anna Medora Baetjer, "Threshold Air Currents." Nina Simmonds, "Observations on Reproduction and Rearing of Young by the Rat as Influenced by Diet."

Missouri: John Lewis Nierman, "The Distribution of the Mineral Elements in the Animal Body as Influenced by Age and Condition."

Ohio State: Waid Wright Tuttle, "A Quantitative Study of the Patellar Reflex."

Stanford: Ernest Herman Brunquist, "Acid Production in the Basic Metabolism of Excised Muscle (Frog) as Affected by Certain Slight Changes in the Liquid Environment; and the Question of Response to Adrenalin." Laurence Irving, "The Carbonic Acid-Carbonate Equilibrium of Sea Water and Its Relation to Respiration and Metabolism in Star-Fish."

Wisconsin: Paul Chesley Hodges, "Estimation of the Cardiac Area in Man."

1924-1925:

Catholic: Gerald Louis Clark, "Early Phases in the Development of the Olfactory Nerve of the Chick."

Chicago: Zacharias Bercovitz, "Studies on the Motility of the Denervated Heidenhain Pouch." Nelles Boyd Laughton, "Studies on the Nervous Regulation of Progression in Mammals." J. Frank Pearcy, "Reflexes from the Colon."

Cornell: Joseph Alma Dye, "Cell Changes in the Central Nervous System Under Various Natural and Experimental Conditions."

George Washington: Everett Monroe Ellison, "The Effects Produced by Ingestion of Extracts of Endocrine Glands."

Harvard: Sherburne Friend Cook, "The Toxicity of the Heavy Metals in Relation to Respiration."

Minnesota: J. Warren Bell, "Vital Capacity of Toxemia of Pregnancy and in Normal Pregnancy." Alice Rupp, "The Metabolism of Muscle Tonus." Maurice Visscher, "The Transportation and Storage of Carbohydrate in the Animal Body."

Missouri: Nollie B. Guerrant, "The Adequacy of Synthetic Rations for Growth of Chicks." Frederick Francis McKenzie, "Correlations of External Signs and Vaginal Changes with the Ovarian Cycle in Swine."

Yale: Howard Horace Beard, "An Experimental Study of Dietary Factors and Dietary Deficiencies in Relation to the Nutrition of White Mice." Marion Spencer Fay, "Nitrogen and Sulfur Metabolism in the Dog." Hymen Samuel Mayerson, "The Effect of Radiation and of Darkness on Metabolism in the Dog." Alice Lincoln Miles, "The Effects of Darkness and of Carbon Arc Radiation on the Physical Characteristics of the Blood."

Doctorates in Science Conferred

	Anatomy			Bacteriology			Pathology			Physiology		
	1922-1923	1923-1924	1924-1925	1922-1923	1923-1924	1924-1925	1922-1923	1923-1924	1924-1925	1922-1923	1923-1924	1924-1925
Brown	..	..	..	2	1	..	..	1	..	..	..	..
California	..	..	..	..	1	..	..	1	..	..	..	..
Catholic	..	..	..	..	..	..	..	..	..	..	..	1
Chicago	3	2	2	5	3	1	1	6	..	4	3	3
Cincinnati	..	..	1	..	..	..	..	..	..	1	..	..
Columbia	1	..	..	4	..	..	..	..	..	1	3	..
Cornell	1	..	..	1	2	..	..	..	1	1	2	1
George Washington	..	..	..	2	..	..	..	..	..	..	..	1
Harvard	..	..	..	..	..	..	1	..	..	1	1	1
Illinois	..	..	..	2	..	1	..	..	..	..	1	..
Iowa	..	..	..	..	..	..	..	..	..	1	..	..
Johns Hopkins	..	..	..	7	..	6	7	3	4	..	2	..
Kansas	1	..	..	..	1	..	..	..	..	..	..	..
Michigan	..	..	..	..	2	1	..	..	..	..	..	..
Minnesota	4	1	1	..	..	..	..	..	..	1	..	3
Missouri	..	..	..	..	..	..	..	..	..	..	1	2
New York	..	..	..	1	..	..	..	..	..	1	..	..
Northwestern	..	..	..	..	..	..	..	..	..	1	..	..
Ohio State	..	..	..	..	..	..	..	..	..	..	1	..
Pennsylvania	..	..	..	..	..	1	..	..	..	..	..	..
Radcliffe	..	..	..	..	..	..	..	..	..	1	..	..
Stanford	..	..	..	..	..	..	..	..	..	..	2	..
Washington Univ., St. Louis	..	1	..	..	..	..	..	..	..	..	..	..
Wisconsin	..	..	..	2	1	4	..	..	..	3	1	..
Yale	..	..	..	4	2	6	2	..	..	3	..	1
Total	10	4	4	30	13	20	11	11	5	19	17	16

Abstracts from Current Literature

Pathologic Physiology

[The abstracts have been prepared by the physicians whose names are signed to them. Unsigned abstracts may be credited to the editorial staff.]

THE EXTRACTION OF A PARATHYROID HORMONE WHICH WILL PREVENT OR CONTROL PARATHYROID TETANY AND WHICH REGULATES THE LEVEL OF BLOOD CALCIUM. J. B. COLLIP, J. Biol. Chem. **63**:395, 1925.

The author has extracted an active principle from the parathyroid glands of oxen which will prevent the symptoms of tetany in parathyroidectomized dogs. The extract is prepared by digesting the glands for one hour with 5 per cent hydrochloric acid at 100 C.; the digest is made alkaline and then freed from protein; the resulting aqueous solution can be used either by mouth, intravenously or subcutaneously. This principle in preventing tetany raises the calcium content of the blood.

When an overdose is used, a syndrome results which is called hypercalcemia by reason of the high calcium content of the blood (from 15 to 18 mg. per hundred cubic centimeters of blood serum the normal content runs from 10 to 11 mg.). The symptoms of hypercalcemia are loss of appetite, dulness, drowsiness, coma and general atony. There was obvious dehydration, as seen from the concentration of blood; when the animals were in the condition of hypercalcemia, it was difficult to withdraw blood from the veins and also to separate the serum. Hypercalcemia can be overcome by sodium bicarbonate. If allowed to persist, it results fatally. Parathyroidectomized dogs do not develop tetany if they receive this extract once or twice daily; if the administration of the extract is discontinued, tetany ensues.

This hormone, affording a means of increasing the calcium of the blood, may prove of value when the calcium metabolism is disturbed.

H. L. HIGGINS.

A METHOD OF OBTAINING BLOOD FROM VEINS, SIMILAR TO ARTERIAL BLOOD IN GASEOUS CONTENT. SAMUEL GOLDSCHMIDT and ARTHUR B. LIGHT, J. Biol. Chem. **64**:53, 1925.

The authors found that blood taken from superficial veins on the back of the hand after the hand had been immersed in hot water (45 C.) had the same percentage of oxygen saturation and carbon dioxid content as arterial blood.

H. L. HIGGINS.

STUDIES IN UROBILIN PHYSIOLOGY AND PATHOLOGY. IV. UROBILIN AND THE DAMAGED LIVER. ROBERT ELMAN and PHILIP D. MCMASTER, J. Exper. Med. **42**:99, 1925.

A variety of evidence is presented, all of which supports the view that in the uninfected animal the intestinal tract is the only place of origin of urobilin, not merely under normal circumstances, but when there is biliary obstruction. Animals rendered urobilin-free by collection of all of the bile from the intubated common duct remain urobilin-free even after severe hepatic injury.

In the experiments urobilinuria was never found after liver damage except when bile pigment was present in the intestine. Thus, for example, it appeared during the first days after ligation of the common duct, but disappeared as the

stools became acholic. When this had happened, a small amount of urobilin-free bile, given by mouth, precipitated a prompt urobilinuria. After obstruction of the duct from one third of the liver, mild urobilinuria was found, but no bilirubinuria. In animals intubated for the collection of the bile only, while the rest flowed to the duodenum through the ordinary channels, liver injury caused urobilinuria, unless indeed it was so severe as to lead to bile suppression, when the urobilinuria ceased almost at once, although the organism became jaundiced.

The evidence presented, when taken with that of previous papers by the same authors, clearly proves that urobilinuria is an expression of the inability of the liver cells to remove from circulation the urobilin brought by the portal stream, with the result that the pigment passes on to the kidney and the urine. Urobilinuria occurs with a far less degree of liver injury than does bilirubinuria.

AUTHORS' SUMMARY.

LIPOIDS AS THE GROWTH-INHIBITING FACTOR IN SERUM. LILLIAN E. BAKER and ALEXIS CARREL, J. Exper. Med. **42**:143, 1925.

The growth-inhibiting action of serum has been shown to be due largely to the lipoids. Serum from which the lipoids have been removed is much less inhibiting to the growth of fibroblasts in vitro than is the original serum, and only slightly more inhibiting than Tyrode solution. The lipoids extracted from the serum are toxic and more inhibiting to the growth of fibroblasts than the original serum. Lipoids extracted from chicken brain, chicken liver, egg and embryonic tissue have likewise an inhibiting action.

AUTHORS' SUMMARY.

AN EXPERIMENTAL STUDY OF THE RELATION OF THE OVARY TO FAT METABOLISM. MONTROSE T. BURROWS and CHARLES G. JOHNSTON, J. Exper. Med. **42**:215, 1925.

The follicular fluid of the ovary contains an active growth stimulating substance and one capable of initiating an active digestion of a foreign fat, which might otherwise remain unabsorbed for an indefinite time in the tissues of these animals.

Whether the substance exciting growth and a digestion of the oil is the same or in any way related to the substance exciting estrus in these animals is not known. That it may be a different substance from the estrus exciting substance is suggested, however, by the fact that a similar excitant of growth and fat digestion has recently been extracted by the same method from the corpus luteum of pits. These extracts of corpora lutea have not excited estrus in spayed rats. In the one rat in which the pure oil was absorbed, the cells did not invade the oil, but the capsule remained cellular, and the oil gradually disappeared from the space. In these experiments in which the active substance was added to the oil the cells have always invaded the oil.

AUTHORS' SUMMARY.

RELATIONSHIP OF HARD WATER TO HEALTH. II. EFFECT OF HARD WATER ON GROWTH, APPEARANCE AND GENERAL WELL-BEING. JOHN T. MYERS, J. Infect. Dis. **37**:13, 1925.

In no instance did white mice, white rats, rabbits, dogs, calves or chicks given distilled water develop better than those given hard water, but the reverse was true under several conditions.

VARIATIONS IN BLOOD AND URINE DIASTASE CONTENTS IN RELATION TO MEALS. I. COHEN, Brit. J. Exper. Path. **6**:173, 1925.

It has been demonstrated by Cohen that the output of diastase into the urine varies greatly. During the day, the rate of diastase output rises and falls without apparently any definite cycle of change. Meals seem to produce an immediate increase in output, which is more marked in some individuals than in others. After the meal effect there is no definite indication whether the output will rise or fall. Readings made during starvation periods have also been found to be irregular. The blood diastase remains at a constantly low level throughout the observation periods, despite the marked changes in the urinary diastase content. It would appear, therefore, that diastase is irregularly absorbed from the bowel, and then is excreted as completely as possible from the blood. In the light of these observations, examination of isolated specimens of urine for clinical purposes would seem to yield very unreliable information. On the other hand, however, the relative constancy of the blood diastase content renders the necessity for any special precautions with regard to meals unnecessary.

HEMOSTATIC EFFECT OF TRANSFUSIONS. H. WILDEGANS, Arch. f. klin. Chir. **136**:627, 1925.

Determination of the coagulation and bleeding time does not yield a satisfactory explanation of the mechanism of hemostasis; but estimation of the thrombin and fibrinogen shows why blood transfusion has a tendency to arrest hemorrhage. This action is observed only if the transfused blood contains thrombin and if the recipient's blood is deficient in thrombin. The amount of fibrinogen present does not seem to play any appreciable rôle in human pathology. Wildegans reports ten cases in seven of which transfusion had an immediate hemostatic effect; in two cases the effect was of short duration, and in one case (bleeding from a larger branch of the hepatic vein) no success was obtained.

THE BLOOD PROTEINS AFTER OPERATION. H. HUECK, Arch. f. klin. Chir. **136**: 774, 1925.

Hueck observed as a general rule that in the postoperative period the blood fibrinogen and the rate of erythrocyte sedimentation are increased, but not necessarily proportionately. The total proteins and the ratio of albumin to globulin are decreased. The surface tension of the serum is not uniformly changed.

EXPERIMENTS ON THE NATURE OF THE THYROID HORMONES AND THE ROUTES OF ESCAPE. Y. TOKUMITSU, Beitr. z. path. Anat. u. z. allg. Path. **73**:585 1925.

Experiments were made to show the presence of a specific hormone in the blood coming from the thyroid gland. The blood from the saphenous vein of the same animal was used in each case as a control. The results were as follows:

1. The blood of the thyroid veins contains a substance which lowers the blood pressure in rabbits through stimulation of the vagus.

2. The substance in small concentration causes a dilatation of the pupil, in larger amounts of constriction. This is a parasympathetic effect.

3. It decreases the tone, frequency and intensity of contractions of the intestinal longitudinal muscle, and supports epinephrin in its inhibiting activity. It decreases the frequency of contraction of the circular muscle, but this effect is prevented, not increased, by atropin and epinephrin. The conclusion is that the hormone acts on the longitudinal muscle by sympathetic stimulation, but on the circular muscle by vagus stimulation.

4. The substance slows intestinal peristalsis in vivo.

No investigation of the lymph was made. The results show that the thyroid hormone has important influence on the vegetative nervous system, sometimes with sympathetic, sometimes with parasympathetic effect. This speaks for a combination of two or more elementary hormones. It is certain only that the blood of the thyroid veins contains hormones, and that thereby a new pathway is shown for the investigation of these substances.

B. R. Lovett.

Death Following Blood Transfusion. R. Lemke, Virchows Arch. f. path. Anat. **257**:415, 1925.

From a study of the necropsy material from two patients who died following blood transfusion, Lemke concludes that in addition to agglutination and hemolysis toxic factors may be active in causing the untoward effects of transfusion. In both of his cases there were focal necroses of the liver and multiple punctate capillary hemorrhages in various tissues and organs.

O. T. Schultz.

Constitutional Factor in Pernicious Anemia. Neuburger, Deutsch. med. Wchnschr. **51**:1557, 1925.

Neuburger finds no evidence of a hereditary factor in pernicious anemia. Four of sixty-five patients believed that the disease had occurred in their family, but investigations showed that they were mistaken. Neuburger also examined the gastric secretion in twenty-nine relatives of fourteen patients. Only one of these subjects had achylia.

Mechanism of Food Storage by the Liver. L. Loeffler and M. Nordmann, Virchows Arch. f. path. Anat. **257**:119, 1925.

From experiments on rats and mice Loeffler and Nordmann conclude that the metabolic functions of the liver, as expressed by the storing and disappearance of foodstuffs, are the result of a reflex mechanism acting on the nervous elements of the hepatic vascular supply.

O. T. Schultz.

Pathologic Anatomy

Studies on Pneumonia Following Naso-Pharyngeal Injections of Oil. G. F. Laughlen, Am. J. Path. **1**:407, 1925.

In the lung oil is actively phagocytosed by endothelial cells which are present in sufficient numbers to dispose of all the oil present and produce consolidation of the lung.

Mild silver protein when given by mouth or introduced into the trachea, does not lead to any reaction on the part of the endothelial phagocytes in the lung.

THE PATHOLOGY OF DIABETES, WITH SPECIAL REFERENCE TO PANCREATIC REGENERATION. SHIELDS WARREN and HOWARD F. ROOT, Am. J. Path. **1**:415, 1925.

A new interpretation is offered of the pathology of the pancreas in diabetes mellitus. The long continued action of an injurious agent (or possibly excessive functional activity) causes a gradual destruction of island, and at times of acinar, cells. New cells are formed to take the place of those destroyed, only to be exposed to the injurious influence with consequent pathologic change. Their injury is followed by the production of still more new cells. Eventually the destructive process wears down the regenerative powers of the pancreas, thus explaining the unfavorable course of the disease. In pneumonia and other infectious diseases, the pancreas readily regenerates after acute injury. The disturbed carbohydrate metabolism giving rise to abnormal fat or protein metabolites may be the cause of the high incidence of vascular disease in diabetic patients.

LESIONS OF CENTRAL NERVOUS SYSTEM IN CANINE DISTEMPER. BENJAMIN ROMAN and CHAUNCEY M. LAPP, Bull. Buffalo Gen. Hosp. **3**:40, 1925.

Of a series of animals, including twenty-seven dogs, one fox and one cat, all said to be suffering from canine distemper, nineteen exhibited changes in the central nervous system, in the form of a disseminated nonsuppurative, inflammatory process of the cord and brain and leptomeninges — meningo-encephalo-polioleukomyelitis. These changes are identical with those found by other investigators.

The changes were mostly found in the nervous but also in the catarrhal and intestinal forms of the disease, so that distemper is regarded as a pathologic anatomic entity.

There is a large group of diseases of man and animals, notably infantile paralysis, which are characterized by similar lesions in the nervous system. The relation of distemper to these diseases cannot be surmised. It can hardly be related to epidermic poliomyelitis, since the latter is apparently not transferable to the dog.

In view of the characteristic anatomic picture of distemper, and in view of its similarity to other diseases not due to ordinary bacteria, the distemper work, with regard especially to B. bronchisepticus, requires revision.

L. HEKTOEN.

CONGENITAL SALIVARY FISTULA OF NECK. R. R. SMITH and W. R. TORGERSON, Surg., Gynec. & Obst. **41**:318, 1925.

The outstanding features of the case reported by Smith and Torgerson are: (1) the presence of the duct since birth with the absence of infection or swelling; thyroglossal ducts are usually closed at birth and later swell and rupture; (2) the absence of ciliated columnar epithelium lining the duct; (3) the history of increased flow of its secretion when eating or thinking of food; (4) the finding microscopically of salivary gland tissue; (5) a groove in the mandible; this indicated that the duct must have been present during early fetal life; (6) the presence of cartilage in an unusual location; this would tend to substantiate the teratoid nature of the whole structure.

PATHOLOGY OF PARALYSIS AGITANS. W. FREEMAN, Ann. Clin. Med. **4**:106, 1925.

Two cases of paralysis agitans, one "idiopathic" and one postencephalitic, were studied in detail by Freeman. In each case there was severe degeneration of the substantia nigra without serious involvement of any other part of the brain. The findings in these two cases support Tretiakoff's contention that the substantia nigra is severely altered in paralysis agitans, and tend to show that this degeneration is the actual cause of the disease. The alterations in other parts of the brain were insignificant in comparison.

AN ACUTE FEBRILE PLEIOCHROMIC ANEMIA WITH HYALINE THROMBOSIS OF THE TERMINAL ARTERIOLES AND CAPILLARIES. ELI MOSCHCOWITZ, Arch. Int. Med. **36**:89, 1925.

A 16 year old girl died after a short febrile illness. The blood examination showed rather marked anemia and 40 per cent. of hemoglobin. At necropsy, numerous hyaline thrombi partly organized were found in the terminal arterioles and capillaries of the heart muscle, and a few in the liver, spleen and kidneys. No description of similar cases could be found in the literature.

B. R. LOVETT.

THE INFLUENCE OF THE AUTONOMIC NERVOUS SYSTEM ON THE FUNCTION OF THE THYROID GLAND. J. HAMILTON CRAWFORD and J. N. J. HARTLEY, J. Exper. Med. **42**:179, 1925.

There is a marked individual variation in the histologic structure of the thyroid gland of rabbits examined at the same season under standard conditions. Although the microscopic appearance varies in different rabbits, the structure of the two lobes in the same animal does not differ. The variations are seen principally in the size and shape of the vesicles and in the quantity and character of the colloid.

With one lobe as a control no histologic changes in the other lobe have been observed following section or stimulation of either the cervical sympathetic or the vagus and its branches.

AUTHOR'S SUMMARY.

THE HISTOLOGICAL CHANGES IN THE THYROID GLAND OF THE RABBIT FOLLOWING LOBECTOMY. J. HAMILTON CRAWFORD and J. N. J. HARTLEY, J. Exper. Med. **42**:193, 1925.

In a series of rabbits the changes which took place in the histology of the left lobe of the thyroid gland after excision of the right lobe have been studied at varying intervals of time. Two days after the removal of one lobe the other lobe showed a slightly increased colloid content, an increased vacuolation of the colloid and a slight increase in the size of the epithelial cells. At the end of a week the vesicles were greatly increased in size and distended with colloid,

and the epithelial cells were flattened, while after from three to four months, signs of compensatory hypertrophy were present.

The changes observed were uninfluenced by division of the vagus or cervical sympathetic.

AUTHOR'S SUMMARY.

GAUCHER'S DISEASE. LUDWIG PICK, Med. Klin. **20**:1812, 1924.

The large clear Gaucher cells arise from the reticular histiocytes of the spleen and lymph glands. They apparently arise also in the bone marrow, from clasmatocytes in Glisson's capsule, in the adventitia, peri-adventitia of the central veins of the lobules, and also from cells in the adventitia of the arterioles in the spleen. Gaucher's disease is a congenital, familial, constitutional, specific disturbance of the metabolism and belongs to the group of congenital metabolic anomalies with Niemann's lipoid cell splenohepatomegaly, alkaptonuria and cystinuria.

A SEWING NEEDLE IN THE RIGHT VENTRICLE OF THE HEART. Z. DOBIJOWA, Trav. d. Inst. d'anat. path. d. Univ. de Pologne **1**:400, 1925.

In a necropsy on a person dying of tuberculosis, a needle was found implanted in the muscle of the right ventricle. The needle pierced the wall, with the point in the pericardium and the blunt end in the cavity of the ventricle. It was surrounded firmly by dense connective tissue. Probably the needle entered the body at some point, passed into a vein of large caliber, and so reached the heart. Clinical observation revealed no sign of the presence of a foreign body in the myocardium.

TRANSPLANTATION OF EPIPHYSIAL CARTILAGE IN MAN. T. OSTROWSKI, Trav. d. Inst. d'anat. path. d. Univ. de Pologne **1**:419, 1925.

Slices of epiphysial cartilage obtained from arthrodesis operations following poliomyelitis were transplanted into the thigh muscles. At various intervals thereafter, during secondary operations, pieces were excised and examined.

After two weeks there was some necrosis of the cartilage, the periosteum was thickened, and was invading the cartilage. After three weeks the rows of cartilage cells had become irregular and broken up into islands by bands of vascular connective tissue. At the end of six weeks the cartilage cells had disappeared, and the cartilage was invaded by bone marrow tissue. After twelve weeks one could no longer distinguish the column formation. The cartilage, invaded by connective tissue and marrow, had taken on the character of osteoid tissue.

The author concludes that autotransplanted cartilage undergoes regressive changes leading to loss of its characteristic structure. Part undergoes necrosis; the rest, invaded by vascular granulation tissue and marrow, is replaced by osteoid tissue. Cartilage transplants are therefore good for filling in anatomic defects, but functional defects cannot be repaired in this way.

B. R. LOVETT.

A CASE OF BILATERAL HYDRONEPHROSIS ON THE BASIS OF ATONY OF THE URETERS. P. KUTSCHERENKO, Centralbl. f. allg. Path. u. path. Anat. **36**:438, 1925.

Necropsy on a patient with bilateral hydronephrosis is described, in which the kidneys, greatly distended, presented the typical picture of atrophy with

chronic inflammation. The ureters and bladder were also much enlarged. No stones or strictures were found. The body also showed signs of infantilism, general poor development and late rickets. In the absence of mechanical causes, the hydronephrosis is attributed to an atony of the ureters. The atony is explained as a result of congenital insufficiency of the ureters; it is purely functional, without anatomic basis. References to other similar instances are given.

B. R. Lovett.

Experimental Fat Embolism. F. Paul and E. Fränkel, Klin. Wchnschr. **4**:1722, 1925.

Rabbits which receive repeated intravenous injections with sublethal amounts of fat show an enormous rise of the nonprotein nitrogen and a considerable drop of the blood sugar. Histologically, all the capillaries contain fat droplets, especially in the renal glomeruli; the liver is free from glycogen, and shows severe degenerative changes. Paul and Windholz undertook their experiments after the death of a woman with the picture of uremia following a fracture of the femur. Necropsy revealed a generalized capillary fat embolism.

Pancreatic Tissue in an Intestinal Diverticulum. W. Steiger, Wien. klin. Wchnschr. **38**:909, 1925.

Steiger reports the case of a man, aged 20, in whom an accessory pancreas in a diverticulum of the lower ileum caused a subacute invagination of the intestine.

The Origin of Myocardial Fragmentation. S. Saltykow, Beitr. z. path. Anat. u. z. allg. Path. **73**:477, 1925.

As the result of his microscopic study of the hearts of two children who died in from four to six hours after food poisoning and of the heart of the mother, who died one month after the poisoning, Saltykow concludes that fragmentation of the heart muscle fiber may occur at an appreciable time before death. He considers the presence of emigrated leukocytes between the ends of the muscle fragments in the cases of early death, and of newly formed connective tissue in a similar situation in the patient dying later, conclusive evidence that fragmentation was a vital phenomenon.

O. T. Schultz.

Contribution to the Pathology of Congenital Hemolytic Icterus. P. Heilmann, Beitr. z. path. Anat. u. z. allg. Path. **73**:493, 1925.

A man, aged 53, had been jaundiced since childhood. The chief pathologic change noted by Heilmann was hemosiderosis of the cells of the reticulo-endothelial system.

O. T. Schultz.

MILIARY NECROSIS OF LIVER IN INFANTS. L. SCHWARTZ, Virchows Arch. f. path. Anat. **254**:203, 1925.

Schwartz studied three instances of liver necrosis observed at necropsy. He holds that it is erroneous to refer to them as the result of pseudotuberculosis. This name had been used because of their resemblance to similar lesions in the lower animals. The changes did not show the slightest resemblance microscopically or histologically to true tubercles. Schwartz regards miliary necrosis as an entity, as an infectious process having its origin in some birth incident and manifesting itself in the first few days of life. Premature infants and twins seem particularly susceptible. The bacteria found were of the diphtheroid type.

THYROID AFTER EXTIRPATION OF THE CERVICAL SYMPATHETIC NERVE. H. KIYONO, Virchows Arch. f. path. Anat. **257**:430, 1925.

Kiyono could detect no changes in the thyroid glands of dogs which had been subjected to unilateral excision of the cervical sympathetic trunk. In one of three fatal cases of exophthalmic goiter, the cervical sympathetic ganglions contained areas of perivascular lymphoid infiltration, which the author believes to be part of the generalized lymphoid hyperplasia present.

O. T. SCHULTZ.

ENDOCRINE ORGANS IN ANENCEPHALY. H. KIYONO, Virchows Arch. f. path. Anat. **257**:441, 1925.

Kiyono made a histologic study of the hypophysis, pineal body, thyroid, parathyroids, thymus, suprarenal and gonads in eleven cases of anencephaly. The only change found was a slight decrease in the size of the suprarenals, the decrease being attributed to an inhibition of growth which manifests itself during the second half of fetal life.

O. T. SCHULTZ.

MIDBRAIN IN DIABETES INSIPIDUS. H. KIYONO, Virchows Arch. f. path. Anat. **257**:477, 1925.

In a case of diabetes insipidus Kiyono found marked round cell infiltration in the tuber cinereum. The posterior lobe of the hypophysis was atrophic, this change being considered secondary to the alterations in the nuclei of the tuber cinereum and neighboring midbrain ganglion.

O. T. SCHULTZ.

PATHOLOGIC HISTOLOGY OF VARICOSE VEINS. S. YAMATO, Virchows Arch. f. path. Anat. **257**:490, 1925.

Yamato examined histologically the veins in thirty-two cases of varicose ulcer of the leg. He believes the primary factor to be a congenital weakness of the vessel wall, due chiefly to deficient formation of elastic tissue. Increased blood pressure acting on such veins is the determining mechanical factor. In all the cases examined there was marked phlebosclerosis, usually associated with dilatation. Changes in the superficial nerves and atrophic disturbances of the skin were common.

O. T. SCHULTZ.

Pathologic Chemistry

CEREBROSPINAL FLUID CHLORIDS. FRANK FREMONT-SMITH and MARY ELIZABETH DAILEY, Arch. Neurol. & Psychiat. **14**:509 (Oct.) 1925.

The cerebrospinal fluid chlorids normally are from 720 to 750 mg. per hundred cubic centimeters expressed as sodium chlorid.

The chlorid content of lumbar, cistern and ventricular fluid is the same in normal fasting subjects.

Cerebrospinal fluid chlorids vary directly with the plasma chlorids, but the quantitative distribution of chlorids between plasma and cerebrospinal fluid is influenced by the protein concentration of plasma and of cerebrospinal fluid, i. e., the greater the difference in protein between plasma and cerebrospinal fluid, in favor of plasma, the greater the difference in chlorids in favor of cerebrospinal fluid. A low and progressively falling spinal fluid sugar (provided the blood sugar is not subnormal), with a low chlorid value (under 620 mg. per 100 c.c.), and a moderate increase of cells, from 400 to 500, most of which are lymphocytes, is characteristic of tuberculous meningitis. In acute purulent meningitis the sugar drops rapidly. A normal or increased sugar content on two or more occasions at intervals of two or more days with normal or with slightly diminished chlorids would speak strongly against tuberculous meningitis and acute purulent meningitis. In epidemic encephalitis, epidemic poliomyelitis, brain abscess or tumor, the sugar is either normal or a little increased and the chlorids normal, except in poliomyelitis, in which it may be moderately depressed.

POST MORTEM BLOOD CHEMICAL DETERMINATIONS. JOHN R. PAUL, Bull. Ayer Clin. Lab. Pennsylvania Hosp. **9**:51, 1925.

Sugar, nonprotein nitrogen, urea nitrogen, creatinin, uric acid, chloride and cell volume determinations have been made on a series of specimens of blood taken after death. By collecting samples from a cadaver immediately after death and again at the end of twenty-four hours, one may estimate the degree of postmortem fluctuation which these constituents of the blood usually undergo.

In a series of nine cases from which at least two samples of blood were analyzed at stated intervals, it was found that during the first twenty-four hours after death the blood sugar rapidly fell to insignificant values, the nonprotein nitrogen rose, the urea nitrogen and creatinin remained fairly stationary, the uric acid and chlorid content seemed to fluctuate irregularly as did also the ratio of cells to plasma volume. The postmortem determination of blood urea nitrogen, if taken within twenty-four hours after death, seems to be of some value in estimating the terminal antemortem blood urea content.

In spite of the great number of complicating and variable factors which confuse the results of postmortem blood chemical studies, valuable information may be gained from some of them. This is particularly true in the case of blood urea nitrogen and creatinin determinations, provided certain precautions are taken. With these determinations an index of terminal renal function may be obtained which is useful to the pathologist in his attempt to place a renal lesion in the anatomic diagnosis in its proper chronologic order, particularly if clinical data on the case happen to be lacking.

HYPERCHOLESTEROLEMIA. I. THE NORMAL BLOOD CHOLESTEROL FIGURES FOR MAN AND FOR THE LOWER ANIMALS. FRED D. WEIDMAN and F. WILLIAM SUNDERMAN, Arch. Dermat. & Syph. **12**:679, 1925.

A review of the literature shows that the various technics have been habitually modified by succeeding workers, and that the values recorded are not consistent. Abstracts of all the technics procurable are given, together with the cholesterol values yielded by each.

A list is submitted indicating the normal range of "whole blood" cholesterol in various animals species, and showing in order which species have the highest values. From this it appears that there is no relation between the dietary habits of animal orders and blood cholesterol content.

CALCIUM CONTENT OF BLOOD AND PUS. F. SCHULZE and E. SCHELLER, Arch. f. klin. Chir. **136**:763, 1925.

Schulze and Scheller found that the blood has regularly a high calcium content in all suppurating diseases, not merely in those cases in which bones are affected. The same is true for the pus. The authors believe that this is one manifestation of the reaction of the organism against the inflammatory process, and that the frequently observed atrophy of the bone in such conditions is caused by a decalcification in order to put the calcium at the wider disposal of the body. The process of final calcification in certain scar formations, consequently, is not a secondary process but one which starts with the very beginning of the inflammation.

LIPASE AND OXIDASE OF LIVER IN PHOSPHORUS POISONING. M. STAEMMLER, Virchows Arch. f. path. Anat. **257**:218, 1925.

Staemmler applied the stalagmometric method in an investigation of the lipase content of the fatty livers of mice poisoned with phosphorus. No detectable difference in the amount of lipase was found in such altered livers as compared with those of normal mice. There is no evidence, therefore, that the deposition of fat is due to a postulated decrease in the fat-splitting enzyme, resulting in lowered fat combustion. Since variation in the rate of oxidation might also be a factor in fat combustion, the oxidase content of the liver was determined by a colorimetric modification of the indol phenol blue reaction. By this method, which does not appear to be free from criticism, a slight increase of oxidative activity was determined in the fatty livers. The author admits that the differences do not warrant definite conclusions, but suggests that there is an actual oxidase deficiency, the increased oxygen formation resulting from the slightly increased activity being insufficient for the combustion of the abnormally large amount of fat brought to the liver.

O. T. SCHULTZ.

VITAL IODIN FIXATION OF BLOOD CELLS. R. STAHL, HORSTMANN and HILSNITZ, Virchows Arch. f. path. Anat. **257**:392, 1925.

The authors applied the Zollikofer method of vital iodin fixation to a study of blood and bone marrow. The glycogen granules of the leukocytes which are stained by the method are absent from the younger precursors of these cells. The nuclei of young erythroblasts are free from glycogen, but this substance appears and increases as the nuclei become older. The method is

considered most valuable as confirming Wright's belief in the origin of the platelets from megakaryocytes, since the latter as well as the platelets contain the same kind of iodin stained masses, which are larger than the granules seen in leukocytes.

O. T. SCHULTZ.

Microbiology and Parasitology

BACTERIOLOGIC DATA ON CHLORIN TREATMENT OF RESPIRATORY DISEASES. H. J. NICHOLS, J. S. SIMMONS and J. P. HITCHENS, Am. J. Pub. Health **15**:699, 1925.

This paper is a summary of the results of bacteriologic studies of the recently proposed chlorin treatment of respiratory diseases. It is part of a combined clinical and laboratory investigation which has been carried on by a board of officers for nearly a year at the Army Medical School and Walter Reed Hospital. The chlorin treatment, in their hands, has given no evidence of even partial sterilization of the mucous membranes of the upper air passages. It does not kill B. prodigiosus sprayed on these membranes. The authors are all of the opinion that, in the doses used, the chlorin is neutralized and becomes inert, and that effective doses are too toxic.

J. A. M. A.

ON THE EXCRETION OF SPECIFIC SUBSTANCES OF TUBERCLE BACILLI IN THE URINE. L. DIENES and J. FREUND, Am. Rev. Tuberc. **11**:35, 1925.

The authors failed to detect any specific substances with tuberculin action in the urine of tuberculous patients. They conclude, therefore, that the skin test observed with the urine of tuberculous persons, as advocated by Wildholz for the diagnosis of active tuberculosis, cannot be interpreted as a specific reaction.

MAX PINNER.

A NOTE ON THE RESISTANCE OF SPECIFIC PROPERTIES OF THE TUBERCLE BACILLUS TO SODIUM HYDROXIDE AND HYDROCHLORIC ACID. L. DIENES and E. W. SCHOENHEIT, Am. Rev. Tuberc. **11**:41, 1925.

Watery extracts from saprophytic acid-fast bacilli are almost equally effective in their complement binding power with tuberculous serum as watery extracts from true tubercle bacilli; but they are much less effective in their tuberculin action. The two immunologic phenomena, complement fixation and allergic reaction, therefore, must be connected with different chemical groups.

MAX PINNER.

THE RESISTANCE OF THE ALBINO RAT TO INFECTION WITH TUBERCLE BACILLI. G. G. ORNSTEIN and M. M. STEINBACH, Am. Rev. Tuberc. **11**:77, 1925.

Albino rats are immune for tubercle bacilli as they do not develop any clinical signs or microscopic evidence of pathologic changes after the introduction of tubercle bacilli; but their organs, and occasionally the blood stream, contain bacilli of undiminished virulence. These infected rats are not sensitive to tuberculin, nor do they display the Koch phenomenon on reinfection. Complement fixing antibodies against Petroff's glycerol antigen were found in normal albino rats and were not increased after inoculation.

MAX PINNER.

TOXIC PRODUCTS OF BACTERIUM ENTERITIDIS AND RELATED MICRO-ORGANISMS. SARA ELIZABETH BRANHAM, J. Infect. Dis. **37**:291 (Oct.) 1925.

Filtrates of fluid cultures of Bacterium enteritidis usually are toxic for rabbits and mice, but not for guinea-pigs, when injected intravenously, but are apparently harmless when given by other routes.

The time between the introduction of the poisonous fluids into the blood stream and symptoms of intoxication seems to bear no relation to the size of the dose, but is constantly about from forty to forty-five minutes, whether the amount given be lethal or sublethal.

The symptoms are restlessness, dyspnea, prostration, often diarrhea, and either death within from one to twelve hours or slow recovery. The acute stage lasts about from thirty minutes to one hour.

The most conspicuous finding at necropsy is a marked general vasodilation, with edema of the lungs, and in many animals, both agglutination and platelet thrombi in the capillaries.

The occurrence of toxicity in cultures is variable, but it may be found in any medium in which the organism grows. The poisons are thermostabile. Toxicity of broth and synthetic medium cultures appears after the number of living cells has reached its maximum and has begun to decrease.

The toxic properties are demonstrable not only in filtrates of fluid cultures, but in autolysates, and with dead and living bacteria.

Toxic materials in dilutions in which no protein can be detected stimulate the production of antibodies. The serum of rabbits immunized with them bestows definite protection on other rabbits when they receive intravenous injections.

Similar poisons are demonstrable with other members of the colon-typhoid group.

The results appear to indicate that the poison demonstrated by these experiments is within the bacterial cells, is set free on cell disintegration, and probably is not a true soluble toxin.

AUTHOR'S SUMMARY.

STUDIES IN EXPERIMENTAL SYPHILIS. IV. THE SURVIVAL OF TREPONEMA PALLIDUM IN THE INTERNAL ORGANS OF TREATED AND UNTREATED RABBITS. ALAN M. CHESNY, JAROLD E. KEMP and ALAN K. POOLE, J. Exper. Med. **42**:33, 1925.

Simultaneous transfers to the testes of normal rabbits of circulating blood, heart muscle, liver, brain, spleen and bone marrow (mixed), inoculated testicle, and popliteal lymph nodes from a series of untreated syphilitic rabbits, demonstrated the persistence of the original infection uniformly in the lymph nodes and less regularly in the liver, mixed spleen and bone marrow, and testis originally inoculated. In one instance the circulating blood was found to be infectious. Transfer of similar tissues from syphilitic rabbits treated with arsphenamin late in the course of the disease failed to disclose syphilitic infection of any of these tissues. In one animal, in which keratitis developed both before and after treatment, the blood, internal organs, and lymph nodes were found to be noninfectious in spite of the fact that the cornea was shown to be the site of a syphilitic inflammation. Transfer of lymph nodes or internal organs of treated syphilitic rabbits is probably the best method of evaluating an antisyphilitic agent, but it must be supplemented by careful observation of treated animals over an appreciable interval of time following treatment.

The results of this study support the idea that failure to reinoculate a treated syphilitic animal does not necessarily mean the existence of the first infection, but might be interpreted as indicating the presence of an acquired resistance which persists in rabbits in which no trace of the first infection can be demonstrated. AUTHOR'S SUMMARY.

STUDIES ON THE ETIOLOGY OF HEARTWATER. I. OBSERVATION OF A RICKETTSIA, RICKETTSIA RUMINANTIUM (N. SP.) IN THE TISSUES OF INFECTED ANIMALS. E. V. COWDRY, J. Exper. Med. **42**:231, 1925.

A gram-negative, intracellular, coccus-like micro-organism was found in cases of heartwater in the three species which are susceptible to the disease; namely, goats, sheep, and cattle. It was absent in the case of control animals, both normal ones and those dying of some other diseases. The presence of this micro-organism was definitely related to the febrile reaction. It was not easily detected in the renal glomeruli and in the small capillaries of the cerebral cortex, but probably occurred throughout the body. The micro-organism was a typical endothelial parasite, being restricted in distribution to the endothelial cells of the smaller blood vessels and to portions of such elements which had broken off into the blood stream. It was never observed to cause injury to the cells other than those incident to mechanical distention through accumulation within them of many individuals in large, densely packed masses which were characteristically spherical. A typical attribute was the presence of several of these masses within the cytoplasms of a single endothelial cell. In view of the association of this micro-organism with heartwater, a disease of ruminants, and thus far the only one in which micro-organisms resembling *Rickettsiae* have been reported, the designation *Rickettsia ruminantium* is proposed. AUTHOR'S SUMMARY.

STUDIES ON THE ETIOLOGY OF HEARTWATER. II. RICKETTSIA RUMINANTIUM (N. SP.) IN THE TISSUES OF TICKS TRANSMITTING THE DISEASE. E. V. COWDRY, J. Exper. Med. **42**:253, 1925.

The evidence offered in the first of these studies indicative of a causative relationship between Rickettsia ruminantium and heartwater is supplemented by the following observations concerning the ticks which carry the disease.

When larvae which had taken no food since hatching were allowed to feed on cases of heartwater, they acquired *Rickettsiae* which appeared to be identical with those in the tissues of animals suffering from heartwater, whereas control larvae hatched from eggs deposited by the same female and fed on normal animals remained free from *Rickettsiae*.

After larvae presumably infective had molted, the resultant nymphae containing *Rickettsiae* in their alimentary tracts when fed on susceptible animals produced in them typical attacks of heartwater, which the control nymphae, devoid of *Rickettsiae*, failed to do. The tissues of animals thus infected on histologic examination were found to contain typical *Rickettsiae*.

AUTHOR'S SUMMARY.

BACTERIAL FACTORS IN PYORRHEA ALVEOLARIS. III. THE ISOLATION OF B. TETANI, B. WELCHII AND OTHER SPORULATING ANAEROBES FROM HUMAN SALIVA. IVAN C. HALL, J. Infect. Dis. **37**:87, 1925.

Sporulating anaerobic bacteria are only occasionally demonstrable in the saliva as spores. *B. welchii, B. tetani, B. bifermentans* and *B. tetanomorphus* have been recovered from saliva and are evidently transient saprophytes in

the mouth. There is no evidence that the sporulating anaerobes have any direct pathologic significance in relation to pyorrhea, but certain species may participate in the deposition of salivary calculus and so indirectly contribute to irritations which in many cases predispose to pyorrhea. Opinion is reserved as to their possible rôle in the decay of dental pulp in caries.

AUTHOR'S SUMMARY.

BACTERIAL FACTORS IN PYORRHEA ALVEOLARIS. IV. MICROCOCCUS GAZOGENES, A MINUTE GRAM-NEGATIVE, NONSPORULATING ANAEROBE PREVALENT IN HUMAN SALIVA. IVAN C. HALL and BEATRICE HOWITT, J. Infect. Dis. **37**:112, 1925.

This paper emphasizes the frequent occurrence in human saliva of a minute, gram-negative, nonsporulating, gas-forming, obligate anaerobe. This organism is mainly responsible for the abundant gas generally seen in primary brain medium cultures from unheated saliva. It was first discovered by Lewkowicz, working with Veillon in Cracow, in 1901, in the mouth of an 8 day old baby, and described under the name *Micrococcus gazogenes-alcalescens-anaerobius;* in accord with modern scientific usage, we suggest the name *Micrococcus gazogenes* (Lewkowicz).

M. gazogenes is a minute diplococcus less than 0.5 mikrons in length and breadth, gram-negative, nonsporulating, nonmotile and obligately anaerobic. These properties have caused it to be overlooked in most of the modern work on the flora of the mouth.

Deep brain is the best medium; no blackening or digestion occurs with or without added iron. Deep agar colonies resemble a tiny buckwheat. Blood-agar surface colonies are small, round, moist appearing, raised, grayish white and nonhemolytic. Gelatin is neither liquefied nor blackened. The only visible change in milk is gas production. Broth cultures become turbid and gassy. No acid is formed from glucose, levulose, sucrose, lactose, maltose, inulin, mannitol, glycerol or salicin. It does not pass through the Berkefeld filter.

It is nonpathogenic directly for guinea-pigs and mice, but it appears to reduce the resistance of rabbits toward other pathogenic microbes.

Ten rabbits immunized by intravenous injection of live cultures produced powerful agglutinins (all over 1:10,000) which distinguished two serologic groups. Group A contained twenty-two strains, group B two strains. Normal rabbits harbor *M. gazogenes,* yet produce no agglutinins except under inoculation, but human beings not infrequently produce low grade agglutinating serums (1:40). The strongest serum came from persons free or practically free from gingival lesions, suggesting an immunologic factor relating to the organism in pyorrhea alveolaris.

AUTHORS' SUMMARY.

OBSERVATIONS ON D'HERELLE'S BACTERIOPHAGE. MAX S. MARSHALL, J. Infect. Dis. **37**:126, 1925.

The purpose was the study of the phenomena of a d'Herelle type or strain of bacteriophage from a quantitative point of view, particularly as regards the mutual relationship between bacterial cells and bacteriophage. Studies of certain corollary features were also made from a quantitative point of view, specifically as regards the absorption of bacteriophage by bacterial cells, the diffusion of bacteriophage through agar and semipermeable membranes, the resistant strains, and the lysed culture as antigen.

A technic was developed for the quantitative estimation of bacteriophage concentration, using an original type isolated by d'Herelle. The normal rate

of multiplication of *Eberthella dysenteriae* (Shiga) during the logarithmic phase of growth was determined, the rate of fission being once every 31.3 minutes in beef infusion broth at 37 C.

The effect of the bacteriophage on this normal logarithmic rate is such as to cause no variation from the normal for a greater or lesser period of time, depending on the concentrations both of the bacteriophage and of the organisms; following this there is a period of lysis. During this exposure of organisms to bacteriophage, a period of stability in bacteriophage concentration occurs, followed by a period of rapid increase, to some extent synchronous with the period of rapid bacterial lysis.

There was found to be a maximum concentration of bacteriophage in beef infusion broth beyond which further lysis of bacterial cells seemed to cause increase. This point of concentration was approximately 225,000,000 units per cubic centimeter.

Experiments on cellular absorption of bacteriophage showed the following: (1) Living bacterial cells sensitive to the lytic action of the bacteriophage absorb bacteriophage from a broth suspension within a period of fifteen minutes at 37 C. Dead cells of the same strain bring about progressive absorption over a period of at least one hour. It was shown that such dead cells probably adsorb bacteriophage rather than absorb it. (2) Tests involving the absorption of bacteriophage by heterologous bacteria indicated absorption from a broth suspension within a period of fifteen minutes at 37 C. with some bacterial strains and none with others. (3) It is concluded that there is no specificity of bacteriophage absorption from the point of view of the accepted bacteriologic grouping, but that there is a specificity from the point of view of susceptibility to lysis by the bacteriophage.

The bacteriophage was found to diffuse 1 mm. in 2 per cent. agar in forty-eight hours, and to diffuse through parchmentized and collodion membranes.

A discussion of the unity in structure of the bacteriophage is presented, and the theory that the agent responsible for transmissible bacteriolysis is a living ultramicroscopic entity is concurred in.

AUTHOR'S SUMMARY.

ANALYSIS OF THE FECAL FLORA IN THIRTY-THREE CASES OF PERNICIOUS ANEMIA, WITH PARTICULAR REFERENCE TO B. WELCHII. L. MARY MOENCH, MORTON C. KAHN and JOHN C. TORREY, J. Infect. Dis. **37**:161, 1925.

A bacteriologic analysis of seventy-two stool specimens from thirty-three cases of pernicious anemia of various durations showed in practically every case an unusually large number of viable organisms, of which *B. coli* streptococci, *B. welchii* and, at times, *B. acidophilus* were the most prominent types. These findings indicated that the flora of the large intestine is of an actively growing, nonproteolytic, fermentative type.

The most significant feature in these examinations would seem to be uniformly high counts for *B. coli* and *B. welchii*. The numbers of both these organisms averaged much higher than for normal persons or for other pathologic conditions. Although streptococci were also numerous, they conformed to the normal intestinal types, no representative of the hemolytic group being encountered.

Pure cultures of *B. welchii* strains were isolated from twenty-six of these cases and subjected to differential tests. Representatives of the four fermentative types of Simonds were encountered, but type 1 occurred with the greatest

frequency (50 per cent.). These several strains differed also in the amount of hemolysin produced. Although most of them were strongly hemolytic, it could not be said that they exhibited in general greater potency in this respect than did strains from normal human intestines. All of the strains tested showed a high degree of pathogenicity, but this is also frequently true for strains from normal sources. It would seem, then, that if these intestinal strains of *B. welchii* are to be brought into etiologic relationship to pernicious anemia, it must be on the basis of their excessive numbers and activities, particularly at levels of the intestine where absorption is active and where they are commonly found only in negligible numbers. In view of Seyderhelm's finding that the flora of the large intestine tends to invade the small intestine in this disease, there is some ground for the latter supposition.

Speculation is offered as to the possible significance of active growth of *B. welchii* at the higher levels of the intestine in the production of the pernicious anemia syndrome in view of its well-known capacity to elaborate a potent hemolysin, an irritating acid and neurotoxic substances.

AUTHORS' SUMMARY.

A DISEASE IN WILD RATS RESEMBLING PLAGUE. N. E. WAYSON, Public Health Rep. **40**:1975, 1925.

There has been observed among the wild rats of Oakland, Calif., and the neighboring cities a disease the gross changes of which resemble those of a plague in rats. The specific factor in the disease is apparently one of the hemorrhagic septicemia group, which produces acute death in inoculated guinea-pigs, wild rats and white rats, with lesions resembling somewhat those of acute plague in these animals.

The practical importance of the disease is the difficulty it interposes in the routine diagnosis of plague in rats. The difficulty arises because of the similarity of plague lesions and those of this disease in the wild rat, and because the presence of the disease in a plague-infected rat frequently results in the premature death of the inoculated test animal before the lesions of plague develop and before the plague organism has become widely disseminated through the tissues.

The sanitary significance of these findings is as yet uncertain, since the pathogenicity of the hemorrhagic septicemia group, other than that of *Past. pestis*, with regard to man is unknown.

ROCKY MOUNTAIN SPOTTED FEVER: VACCINATION OF MONKEYS AND MAN. R. R. SPENCER and R. R. PARKER, Public Health Rep. **40**:2159, 1925.

Vaccine is prepared by grinding internal organs of ticks (*D. andersoni*) that have fed on infected guinea-pigs, diluting the emulsion so that each cubic centimeter represents the viscera of one tick, and adding 0.5 per cent. of phenol. After settling, the supernatant fluid is used as vaccine. The vaccine protected guinea-pigs, rabbits and monkeys; it produced no severe reactions in human beings, and the serum of vaccinated animals and persons contained virus—neutralizing substances. The cause and outcome of a case of spotted fever developing eight days after the first dose of vaccine suggested that the infection had been modified.

NON-GLUCOSE-FERMENTING BACTERIA AND INSULIN. ARTHUR ISAAC KENDALL, J. Infect. Dis. **37**:329 (Oct.) 1925.

The results are wholly negative. There is no suggestion in them that insulin, under the conditions imposed by the method employed, stimulated these several non-glucose-fermenting bacteria to utilize this sugar with the production of acid.

AUTHOR'S SUMMARY.

THE RÔLE OF THE MONOCYTE IN TUBERCULOSIS. R. S. CUNNINGHAM, F. R. SABIN, L. SUGIYAMA and J. A. KINDWALL, Bull. Johns Hopkins Hosp. **37**:231, 1925.

As a result of extensive studies, the authors offer "as a new concept for an experimental attack on the problem of tuberculosis the theory that the tubercle bacillus attacks one specific type of cell—the monocyte." Hematologic studies on rabbits, using the ordinary film method and supravital staining with neutral red and janus green, established the fact that the ratio of monocytes to lymphocytes is normally 1 to 2.97; in rabbits with a progressive tuberculosis the average ratio was 1 to 0.79, while "in rabbits with a consistently high resistance to the disease" the ratio was 1 : 3.56. A tuberculous infection not only increases the number of monocytes in the blood, but brings about characteristic morphologic changes in these cells: "there is an enormous increase in the number, accompanied by a decrease in the size, of the fine particles that make the rosette of the normal cell." In acute tuberculous infections monocytes of the peripheral blood were found to be infected. Not only the mature monocytes of the streaming blood become increased, but equally the parent cell of the monocyte, the reticular cell. The transformation of monocytes into typical epithelioid cells and into giant cells takes place in monocytes which have ingested bacilli. The authors believe that the monocyte and its derivatives, epithelioid and giant cells, are the only cells in the animal body in which the tubercle bacillus leads a truly parasitic life and that the power of these cells to destroy the engulfed bacilli is—if it exists at all—limited; there is evidence from histologic observations on living cells that bacilli multiply within in the cell body. The first effect of a tuberculous infection on the monocytic system must be a chemical action, since reticular cells and very young monocytes have never been found to contain bacilli.

MAX PINNER.

INFLUENCE OF SITE OF INOCULATION ON INFECTIVITY OF ANTHRAX BACILLI AND PNEUMOCOCCI. P. N. PANTON and T. H. C. BENIANS, Brit. J. Exper. Path. **6**:146, 1925.

Panton and Benians summarize their observations as follows: Death following transcutaneous inoculation of anthrax in rabbits does not appear to depend solely on the soiling of the skin by the needle in passage. The receptivities of the skin and the subcutaneous tissues of the rabbit for anthrax infection are different. A dose fatal in the skin can be tolerated under the skin. Subcutaneous inoculation is followed by immunity both to dermal and to transcutaneous inoculation in a small proportion of animals. This immunity is again lost subsequent to dermal inoculation. The white mouse is insusceptible to pneumococcal infection of the skin, highly susceptible to transcutaneous inoculation, and relatively insusceptible to purely subcutaneous infection. Some degree of

immunity appears to follow both dermal and subcutaneous inoculation. The rabbit shows marked individual susceptibility to pneumococcal infection of the skin. The susceptible animal develops an acute inflammation of the skin, and no dermal immunity follows. These experiments suggest the possibility that in the experimental production of anthrax infection in rabbits and of pneumococcal infection in mice by transcutaneous inoculation a double factor is involved, both skin and subcutaneous tissues playing a distinct part.

J. A. M. A.

SPECIFIC PRECIPITATING SUBSTANCE FROM TUBERCLE BACILLI. P. P. LAIDLAW and H. W. DUDLEY, Brit. J. Exper. Path. **6**:197, 1925.

Glycogen has been isolated by Laidlaw and Dudley from tubercle bacilli, likewise a carbohydrate complex of the nature of a gum. This gum gives specific precipitation with immune serum. The gum is not a true antigen, since it fails to induce the formation of antibodies. The significance of these findings is discussed.

LYMPHATIC PSEUDOTUBERCULOSIS. G. DESSY, Bol. Inst. Sieroterapico Milanese **4**:123, 1925. STUDY OF A BACILLUS OF PSEUDOTUBERCULOSIS. G. DESSY, Ibid. **4**:133, 1925.

The organism studied by the author resembled the bacillus of pseudotuberculosis rodentium of Pfeiffer Wellmann. Specific agglutinins were found in the blood of guinea-pigs, injected subcutaneously, and the organism was recovered in the circulation. Intradermal tests with the soluble toxin gave positive results. No active or passive immunity could be produced. A state of hypersusceptibility was demonstrated in animals which had received injections of dead or living organisms. It was not possible to transfer this hypersusceptibility passively.

B. R. LOVETT.

THE PROBLEM OF TRANSMISSIBLE MICROBIC AUTOLYSIS OR OF BACTERIOPHAGE. JULES BORDET, Ann. de l'Inst. Pasteur **39**:717, 1925.

No final explanation of the nature of the phenomenon of bacteriophagy has been offered, and because of the confusion necessarily existing in the abundant literature on the subject, Bordet has brought together in this article the known facts concerning the nature of the principle and the arguments substantiating his theory. He believes the lytic action to be due to an autolysis, resulting from a displacement of the equilibrium between assimilation, which creates new living material, and metabolism, which breaks down this material. It is a property of a normal bacterial body, but one which under certain conditions or influenced by certain individual bacteria can manifest itself as a morbid function. This physiologic property can be communicated to normal susceptible persons, and is regenerated by the fact that it is active. Bordet compares the conception to the action of a thrombin which when added to a plasma accelerates the production of new thrombin at the expense of materials contained in the plasma. He believes that lytic principles may intervene in the evolution of a culture as a factor of antagonism as well as equilibrium, giving predominance to certain types.

G. B. RHODES.

A Clinical and Experimental Study of a Case of Herpes of Finger. S. Nicolau and P. Poincloux, Ann. de l'Inst. Pasteur **38**:977, 1924.

A herpes of the forefinger was studied in its various recurrences during the last five years, and a virus was isolated during the exacerbations. During two of these recurrences, the patient had mild symptoms of central nervous system involvement and at such times the isolated virus showed greater neurotropic properties in animals than did the virus isolated from vesicles which were not accompanied by neurologic symptoms. The authors discuss the possibility of this virus being at a transitional stage between one causing herpes of the skin and one capable of producing epidemic encephalitis.

Pathogenesis of Lambliosis. V. Gaivoronsky, Rev. de microbiol. et d'epidemiol. **4**:111, 1925.

The attempt of several authors to attribute to *Lamblia intestinalis* an etiologic rôle in diseases of the biliary tract has given a special interest to the study of this protozoon. Gaivoronsky examined the duodenal contents in seventy-six cases of gastric and biliary disease, and found *Lamblia* in thirteen of them. One patient had a cholecystitis. At operation no gross lesions were found; there were no *Lamblia intestinalis* in the gallbladder, but many in the duodenum. In another patient with chronic enteritis and alimentary edema, who died of pneumonia, the parasites again were found in the small intestine but not in the gallbladder.

The author considers the part of *Lamblia intestinalis* in biliary disease uncertain. The intestine is a place in which it is difficult to discover the true pathogenic agent. However, the abundance of these parasites and their ability to become implanted there must influence absorption, elimination and nutrition, while the pains and intestinal symptoms suffered by these patients seem to indicate that *Lamblia intestinalis* cannot be entirely indifferent for man.

B. R. Lovett.

Experimental Gonococcic Ophthalmia in the Rabbit and Guinea-Pig. E. Korobkova, Rev. de microbiol. et d'epidemiol. **4**:112, 1925.

Ocular lesions were produced in rabbits and guinea-pigs by putting bile in both eyes, and three or four hours later, a concentrated emulsion of gonococci in one eye. After from twenty-four to sixty hours, edema of the conjunctiva followed by purulent discharge appeared in 75 per cent. of the rabbits and 50 per cent. of the guinea-pigs. Later there were opacity and ulceration of the cornea. Smears and cultures of the pus showed gonococci. In the guinea-pig the process lasted about a week, ending in complete recovery. In the rabbit there was an acute form, lasting from sixteen to eighteen days, with recovery, and a slower, more destructive form often ending with loss of vision. No immunity was conferred either on the same or on the other eye; after recovery the eye could again be infected, with the same results. The blood contained no agglutinins.

B. R. Lovett.

On the Method of Morphological Studies of Malaria Parasites. I. Ioff, Rev. de microbiol. et d'epidemiol. **4**:114, 1925.

Morphologic investigations of malarial parasites for the last fifteen years have had for their purpose the study of new varieties, atypical forms, etc. The

only method employed was that of dry smears. The author points out that the rapid and slow methods of drying blood smears produce atypical morphologic pictures of the parasites.

Young parasites in slowly dried smears appear as regular, sharply outlined rings, with a compact, dark grain of chromatin, while in rapidly dried ones, the protein has irregular ameboid shapes and the chromatin is larger, looser and paler. The rate of drying influences the compactness of the chromatin in the daughter nuclei. Other changes in appearance are indicated, with the mistakes that may be made in consequence.

The author concludes that in studying the morphology of malaria parasites one must not forget that the dry smear method is imperfect, and the results depend in part on the method of drying employed.

B. R. LOVETT.

THE INFLUENCE OF AIR AND OF GLYCEROLE ON FIXED VIRUS. N. I. GRJASNOV, Rev. de microbiol. et d'epidemiol **4**:116, 1925.

Remlinger obtained the fixed virus of rabies in the dried state without attenuation of the virulence. It was thought that while slow drying does cause attenuation, rapid drying is without such effect. The author found that fixed virus dried slowly and protected from the air remained virulent after seventeen days. Hence it is apparently not drying but the oxygen of the air that causes attenuation. Glycerol conserves the virulence merely by protecting the virus from the air. It would be better to discontinue the old method of attenuation by drying (really oxydation) and to use the method of attenuation in glycerol proposed by Remlinger which is accomplished more slowly and in a more uniform manner.

B. R. LOVETT.

CONTRIBUTION TO THE STUDY OF THE NATURE AND SIGNIFICANCE OF THE AMATO BODIES. P. PAULI, Sperimentale **79**:871, 1925.

Amato, in 1913, described certain granulated bodies within the polymorphonuclear leukocytes in scarlet fever. Pauli regards these bodies as distinct from those described by Doehle, Mallory and others. Similar bodies may be found also in typhus fever, chickenpox and other eruptive diseases. The view is advanced that these bodies may be infectious agents.

POLYMORPHISM OF THE TUBERCLE BACILLUS. MYCELIUM-LIKE AND BRANCHED FORMS. F. ARLOING and A. DUFOUNT, Rev. Tuberc. **6**:517, 1925.

In cultures of one of Arloings homogenous strains of tubercle bacilli on Vaudremer's medium, long filament-like bacillary forms were obtained and mutants which showed a mycelium and true branching. The acid-fastness of these forms is markedly decreased. When these mutants are transferred to the usual mediums, they revert to the classical Koch type.

MAX PINNER.

EXPERIMENTAL INOCULATION OF HERPES ZOSTER IN HUMAN BEINGS AND THE RELATION OF HERPES ZOSTER TO VARICELLA. KARL KUNDRATITZ, Monatschr. f. Kinderh. **29**:516, 1925.

Kundratitz was able to transmit herpes zoster from one child to another by inoculating the contents of the vesicles into the skin. In an occasional case the resulting reaction resembled varicella although usually the lesions remained

localized. These children who had already had varicella could not be inoculated. This is the first time that herpes zoster has been produced in this fashion, and is of particular interest in view of the hypothesis that the disease is of nervous origin.

PULMONARY TUBERCULOSIS WITH CAVITY FORMATION IN INFANTS. A. GHON, Ztschr. f. Tuberk. **43**:3, 1925.

Ghon analyzes 890 necropsies on children with tuberculosis; 203 of these were in the first year of life; of these, 191 had a primary pulmonary infection, sixty-five had definite cavities and twenty-four caseous foci tending to cavity formation. Ninety-one per cent of the cases with cavity showed hematogenous propagation of the tuberculous infection. Forty-five had only one cavity. The size of the cavities varied from the size of a pea to a cavity which extended almost throughout the whole right upper lobe of an infant 10 months of age. The cavities may either be the result of the primary focus (primary cavity) or they may arise from metastatic processes or from a superinfection (secondary cavity). The comparative frequency of the localization of the cavities is the same that Ghon has found in his material for the site of the primary focus; i. e., in order of frequency: right upper lobe, left upper lobe, left lower lobe, right lower lobe, right middle lobe.

MAX PINNER.

THE ESTIMATION OF THE LIPASE IN THE SERUM OF TUBERCULOUS CHILDREN. E. HECKER and J. VIERHAUS, Beitr. z. klin. Tuberk. **61**:303, 1925.

The amount of serum lipase does not allow of a prognosis in tuberculous children.

MAX PINNER.

ASPERGILLUS GANGRENE OF THE LUNG. A. ESSER, Virchows Arch. f. path. Anat. **257**:4, 1925.

In the upper lobe of the right lung of a man, aged 55, who died of progressive cachexia, there was found a chestnut-sized area of gangrene, from which *Aspergillus fumigatus* was cultivated. Histologically the tissue reaction was not characteristic. Cachexia and death were ascribed to the action of toxins developed in the lesion; the latter was held to be a primary mycosis.

O. T. SCHULTZ.

THE SPECIFICITY OF THE TUBERCULIN REACTION AND ITS HISTOLOGIC CHARACTER. W. BLUMENBERG, Beitr. z. klin. Tuberk. **61**:509, 1925.

Blumenberg injected tuberculins and colon bacilli into the skin of normal and tuberculous persons and excised the site of injection after various intervals. The histologic changes following these injections is essentially the same in the case of colon bacilli as in the case of tuberculin: a tuberculoid formation with epithelioid cells and Langhans' giant cells. The two reactions are only quantitatively different. The author concludes from these studies that the tuberculin reaction is not specific.

MAX PINNER.

BACTEREMIA CAUSED BY DIPHTHERIA BACILLI. ROOSEN RUNGE, Virchows Arch. f. path. Anat. **254**:379, 1925.

The literature indicates that in deaths from diphtheria the occurrence of diphtheria bacilli in various organs is not associated with specific changes. Even when diphtheria bacilli have been found in the blood stream at necropsy, it has been shown that avirulent forms predominate. Bernard and Paneth lent support to this view by demonstrating that diphtheria bacilli lost their virulence on injection into the blood streams of dogs and guinea-pigs. Runge reports the case of a child, aged 2½ years, in whom diphtheria bacteremia was demonstrated. The child became ill with an upper respiratory infection, followed by swelling of the feet, generalized edema, ascites, numerous petechial hemorrhages of the skin and a temperature ranging from 38 to 39 C. (100 to 102 F.). A systolic murmur was audible over the entire heart. The blood picture was one of anemia with leukocytosis. Death occurred in three days. Blood culture at entrance and death showed diphtheria bacilli. Necropsy showed septic endocarditis of the tricuspid valve, hydrothorax, hydropericardium and hemorrhagic infarcts in the right lower lobe. Runge attempts to explain the profuse growth of bacteria in the blood stream on the basis of the work of Lorentz, who was able to vary the activity of growing diphtheria bacilli in vitro by changing the acidity of the culture medium. In this instance, the lesion on the venous side of the heart may have brought about such change in vivo.

SCHWARTZ.

CONTRIBUTION TO THE KNOWLEDGE OF BACTERIOPHAGE-LIKE PHENOMENA. CURT SONNENSCHEIN, Centralbl. f. Bakteriol., Parasitenk. u. Infektionsk. I. O. **95**:257, 1925.

The author isolated a fungus of the class of *Monilia,* which showed in the surface growth sharply circumscribed spots of clearing. In these places the surface was moist and glistening, in contrast to the dry and dull surface of the remaining colonies. The picture resembled that due to d'Herelle's bacteriophage, but was caused merely by a change in form of the organisms. Fresh cultures made from the clear spaces revealed the organisms in their original form again.

B. R. LOVETT.

THE BACTERIOPHAGE IN CHILDREN'S PYELITIS. F. N. SICKENGA, Nederlandsch Maandschr. v. Geneesk. **13**:141, 1925.

Sickenga found a bacteriophage constantly in the urine in four of twenty-six cases of colon bacillus pyelitis in children from 5 weeks to 3½ years old. The bacteriophage was found occasionally in twelve others, but not at all in ten others. The course of the pyelitis did not seem to be modified by the bacteriophage, and none was ever found in urine or feces that was strong enough for complete lysis of the corresponding bacillus in broth culture.

Immunology

QUANTITATIVE RELATIONS BETWEEN ANTIGEN AND ANTIBODY IN THE PRECIPITIN REACTION. H. W. CROMWELL, J. Infect. Dis. **37**:321 (Oct.) 1925.

When two or more specific precipitating serums are tested against the same lot of antigen, they all react with the same dilution of the antigen regardless of the strength of the serums, provided a simple antigen is used.

The determination of the point of disappearance of a recognizable precipitate on increasing the dilution of the antigen does not, therefore, give direct evidence as to the strength of the antiserum.

The point of maximum precipitation when a single dilution of the antiserum is tested against the various antigen dilutions represents an approximately equal number of units of antigen and antibody. On the basis of this act, then, one can calculate the antibody content of the serum with considerable accuracy when, by test, the antigen titer and point of maximum precipitation have been determined with one dilution of the serum. This is true, provided a simple antigen is used in the test.

The exact quantitative relations do not obtain when a complex antigen like sheep serum is used. The antigen titer is not constant, but varies in a general way with the antibody titer of the serum. The maximum precipitate occupies a whole zone, in which it is often impossible to pick out one tube showing heavier flocculation than the others. It is not possible, therefore, to make calculations that would agree even approximately with experimental results.

The neutralization of antigen by its specific antibody in the precipitin reaction seems, like the toxin-antitoxin reaction, to follow the law of multiple proportions. Is it not possible that when further study is made other types of antigen-antibody reactions will be found to follow this same law?

AUTHOR'S SUMMARY.

IMMUNOLOGICAL REACTIONS OF THE ISOLATED CARBOHYDRATE AND PROTEIN OF PNEUMCOCCUS. OSWALD T. AVERY and HUGH J. MORGAN, J. Exper. Med. **42**:347, 1925.

The data presented in this paper indicate that the isolated carbohydrate and nucleoprotein constituents of pneumococcus differ both serologically and antigenically one from the other. Moreover, each of these fractions of the cell separately exhibits immunologic properties distinct from those manifested by the whole organism of which they form a part.

The carbohydrate is a protein-free polysaccharide, and as such is devoid of the property of stimulating antibodies. Although in the free state, dissociated from other cellular substances, it is nonantigenic, in this form it still retains the property of reacting specifically in antipneumococcus serum of the homologous type. Further, this nonprotein constituent is not reactive with antiprotein serum; in other words, neither pneumococcus carbohydrate nor protein as separate antigen gives rise to antibodies with specific affinities for the carbohydrate or so-called soluble specific substance of pneumococcus.

The nucleoprotein of pneumococcus, on the other hand, is antigenic. Immunization with this cell constituent gives rise to immune serum which precipitates solutions of pneumococcus protein without regard to the type from which it is derived.

The interrelations of the carbohydrate and protein of pneumococcus as they exist in the intact cell to form the complete antigen, and the interpretation of the differences in the antigenic properties of the whole bacterium as contrasted with those of its component parts, are reserved for discussion in a subsequent paper.

AUTHORS' SUMMARY.

THE ANTIGENIC PROPERTIES OF SOLUTIONS OF PNEUMOCOCCUS. OSWALD T. AVERY and JAMES M. NEILL, J. Exper. Med. **42**:355, 1925.

Intact pneumococci, possessing specific antigenic powers unimpaired by cultural or other procedures, give rise to agglutinins for organisms of the homologous type and to precipitins for the type-specific carbohydrate derived from them.

Solutions of pneumococci free from all formed elements, but containing the carbohydrate and protein of the original cell, fail to stimulate the formation of type-specific antibodies. Serums prepared in this manner do not react with the carbohydrate constituent of the cell and do not agglutinate organisms of the homologous type. The loss of this antigenic function is related to changes incurred during dissolution of the bacterial cell.

Solutions of the cellular substances of pneumococcus, although lacking the specific antigen of the whole cell, induce the formation of antibodies reactive with pneumococcus protein regardless of the type from which the latter is derived.

AUTHORS' SUMMARY.

IMMUNOLOGICAL RELATIONSHIPS OF CELL CONSTITUENTS OF PNEUMOCOCCUS. OSWALD T. AVERY and MICHAEL HEIDELBERGER, J. Exper. Med. **42**:367, 1925.

In this paper the general immunologic significance of the intact pneumococcus cell and of its protein and carbohydrate components is discussed.

THE IMMUNOLOGICAL RELATIONSHIPS OF STREPTOCOCCUS VIRIDANS AND CERTAIN OF ITS CHEMICAL FRACTIONS. I. SEROLOGICAL REACTIONS OBTAINED WITH ANTIBACTERIAL SERA. REBECCA C. LANCEFIELD, J. Exper. Med. **42**:377, 1925.

Agglutination and precipitation by the specific substance of *Streptococcus viridans* are parallel phenomena. Separate specific substances have been extracted from strains which are distinct by ordinary serologic tests. Preliminary chemical examination indicates that the specific substances may be complex carbohydrates.

A close relationship between nucleoproteins from different strains of *Streptococcus viridans* is suggested by the existence of a certain amount of cross precipitation and a larger degree of cross complement fixation. But the occurrence of stronger reactions with homologous than with heterologous nucleoproteins indicates that there is some degree of individual difference in proteins from separate strains.

Two distinct antibodies are present in the serum antibacterial for *Streptococcus viridans:* one of high titer implicated in the parallel phenomena of agglutination and precipitation by the soluble specific substance, the other usually of low titer and involved in precipitation by nucleoproteins but probably little, if at all, in agglutination.

AUTHOR'S SUMMARY.

DIPHTHERIA IMMUNITY. EFFECT OF REPEATED INJECTIONS OF AVIRULENT DIPHTHERIA BACILLI, B. HOFMANNI AND B. XEROSIS IN GUINEA-PIGS. M. J. ROSENAU and G. HOWARD BAILEY, J. Infect. Dis. **37**:97, 1925.

The object was to determine whether avirulent diphtheria bacilli are able to stimulate antitoxin production and thus account for the acquired immunity to diphtheria which most persons develop with maturity. Seventeen different strains of avirulent cultures and cultures of related organisms, such as *B. hofmanni* and *B. xerosis* were injected into guinea-pigs over a long period of time. The Schick test remained positive for all these guinea-pigs, and when the final test was made they showed no immunity to diphtheria toxin.

The study emphasizes the essential difference between the so-called avirulent diphtheria bacilli and the true Klebs-Loeffler organism. Not only did the avirulent strains fail to induce immunity, but their agglutination reactions also

showed that there is a wide immunologic gap separating them from the diphtheria bacillus. Some of these so-called avirulent strains have pathogenic properties. AUTHORS' SUMMARY.

ETIOLOGY OF INCRUSTED CYSTITIS WITH ALKALINE URINE. BENJAMIN H. HAGER and THOMAS B. MAGATH, J. A. M. A. **85**:1352, 1925.

The deposition of inorganic salts in cystitis with alkaline urine appears to be due to a gram-negative bacillus (*Salmonella ammoniae*), which produces a urease that converts urea into ammonia, the resulting alkalinity precipitating the calcium magnesium and ammonium salts. This process may develop into any form of cystitis. The condition can be produced experimentally.

ACQUIRED IMMUNITY IN SILKWORMS. R. W. GLASER, J. Immunol. **10**:651, 1925.

Acquired immunity toward a "Flacherie"-like disease was produced in a large number of silkworms by injecting killed cultures of the specific bacillus. Subsequent infection by feeding the living bacillus rarely produced the disease. A single treatment with vaccine so employed, perhaps, demonstrates some immunizing effect, but more than one treatment is necessary to obtain a pronounced effect.

Acquired immunity against this disease was not produced by feeding vaccine, followed by feeding the living culture; nor was any noticed by injecting the vaccine, followed by the inoculation of a minimum lethal dose of the living culture. S. A. LEVINSON.

THE HEAT PRODUCED BY REACTIONS OF ANTIGENS WITH ANTIBODIES. S. BAYNE-JONES, J. Immunol. **10**:663, 1925.

The differential microcolorimeter of A. V. Hill was used in order to measure the heat produced by the combination of diphtheria toxin with antitoxin and by the agglutination of bacteria by an immune serum. The observations on the heat produced by the agglutination of bacteria by an immune serum have only a qualitative significance, as it is impossible to reduce these to any satisfactory quantitative terms. Heat is liberated during this reaction in two periods: the first corresponds to the period in which the antigen and antibody combine; the second corresponds to the period of mechanical flocculation of the bacteria. S. A. LEVINSON.

REMARKS ON CONDITIONS NECESSARY TO AROUSE THE ALLERGIC STATE IN TUBERCULOSIS AND ON IMMUNITY THROUGH FIXATION OF BACTERIA. A. K. KRAUSE, Tubercle **7**:29, 1925.

Tuberculin sensitiveness is strictly dependent on tubercles in the animal body, whether these be produced by a true infection or by the introduction of dead bacilli. The degree "varies directly with the extent and intensity of the disease"; it "increases with progressive disease"; it "diminishes with the healing of the disease" and "is increased by reinfection." Tuberculin sensitiveness or tissue allergy is essentially different from, and in its genesis independent of, anaphylaxis against the proteins of the tubercle bacillus; the latter can be induced easily by the injections of these proteins without the formation of tubercles. The Koch phenomenon is a manifestation of high allergy; a lysis of the tubercle bacilli of reinfection at the site of the acute inflammatory reaction has never been satisfactorily demonstrated. But the bacilli of reinfection spread very much less rapidly than the bacilli of the first infection. It is,

therefore, an experimentally fully supported hypothesis of the mechanism of immunity in tuberculosis that tubercle formation induces the state of allergy, which is a cellular condition and not necessarily associated with the production of serum antibodies; and that the most significant manifestation of this state of allergy is the great retardation in the spread of reinfecting tubercle bacilli. Opie's finding on the mechanism of Arthus' phenomenon suggests that the local fixation of antigens in immune animals is a general biologic principle.

MAX PINNER.

CHOLESTERINE AND HEMOLYSIS. A. H. ROFFO, Bol. del. Inst. de Med. Exper. **1**:419, 1925.

Following the discovery of the relation of natural heterohemolytic activity to the age of the animal, Roffo investigated the cholesterin content of the serum and found that there is a notable increase in the lipoid as age advances and the hemolytic activity increases. There is a still more striking corollary between the large amount of cholesterin in the serums of animals of the species containing strong heterohemolysis, such as the eel, and small cholesterin content in guinea-pig serums which are not markedly hemolytic. Eel serum contains eighteen times as much cholesterin as guinea-pig serum, and other species show equally consistent correlation.

NONSPECIFIC STIMULATION OF ANTIBODIES: THE EFFECT OF MANGANESE ON AGGLUTININS. E. S. HORGAN, Brit. J. Exper. Path. **6**:108, 1925.

Some investigators hold that the quantitative production of certain antibodies, especially antitoxin, can be increased by the injection of various metallic salts into the immunized animal. Manganese and beryllium have given the best results. There have been conflicting reports concerning the influence of these metals on the production of other antibodies. The author studied the effects of the intravenous injection of manganese on the formation of typhoid agglutinins in rabbits. In none of the animals did the injections of inorganic manganese prevent the fall in agglutinating titer from the original high point produced by the injection of typhoid bacilli. Three of six animals showed a slight secondary rise in titer when the manganese was given subsequent to this postapex fall. A commercial preparation of manganese in colloidal form gave negative results. The author suggests that the reaction to the nonspecific stimulation of the manganese depends more on the potentialities of the animal than on the chemical.

L. A. HOAG.

THE ANTIGENIC PROPERTIES OF PRECIPITATES PRODUCED BY THE INTERACTION OF DIPHTHERIA TOXIN AND ANTITOXIN. PERCIVAL HARTLEY, Brit. J. Exper. Path. **6**:112, 1925.

The diphtheria toxin-antitoxin mixtures commonly used for the production of active immunity cause local reactions because of nonspecific poisonous substances from the culture medium, horse serum and bacterial protein. It is possible to secure an antigenic flocculent precipitate almost entirely free from these interfering substances when diphtheria toxin and antitoxin are mixed under proper conditions, as outlined by Ramon. This precipitate is toxic, neutral or antitoxic, depending on whether it was precipitated from an underneutralized, exactly neutralized or overneutralized mixture. The substance is insoluble in salt solution, and can have nearly all the contaminating

material removed by repeated washing in this fluid. Guinea-pigs that have received injections with the washed precipitates from overneutralized mixtures developed an immunity to diphtheria toxin and had demonstrable antitoxin in their blood. The antigenic power of the flocculent precipitate varied inversely with the amount of antitoxin present in the mixture from which the precipitation occurred. The most active preparation was obtained from a mixture which was slightly toxic for guinea-pigs.

L. A. Hoag.

Intradermal Test for Hydatid Disease. N. Sette, Policlinico **32**:1175, 1925.

Sette presents evidence that the fluid of a hydatid cyst can be filtered through porcelain and heated to 70 C. without losing its specific power to induce a typical reaction when injected intradermally in a subject infested with the echinococcus. He evaporates 150 c.c. of hydatid cyst fluid and mixes the residue with 10 c.c. of 0.9 per cent. sodium chlorid solution and 20 c.c. of glycerol; 0.1 c.c. of this fluid is used for the Casoni intradermal and subcutaneous tests. Both this extract and the filtrate proved durable up to a year, in his experience. Even with twice the amount he was unable to elicit a positive response in forty-six controls.

Echinococcus Anaphylaxis. J. H. Botteri, Wien. klin. Wchnschr. **38**:1186, 1925.

The author has studied the practical diagnostic significance of immune reactions in echinococcus patients. The intracutaneous injection of hydated fluid into the forearm gives rise to marked specific local inflammatory reactions in infected persons. Considerable edema of the subcutaneous tissue may develop. The hydated fluid retains its antigenic action for a long time if preserved with a little chloroform. There is a local eosinophilia in positive cutaneous reactions. This skin reaction may be used in cattle also.

The Unity of Pneumococci and Streptococci. Investigations in Pneumococcus Infections of Man. E. Berger and B. Engelmann, Deutsch. med. Wchnschr. **51**:1317, 1925.

The authors conclude from their work in the Koch Institute in Berlin that in the course of human infections pneumococci may undergo modifications with the formation of streptococci. The results support the unity of pneumococci and streptococci. Streptococcus mixed and secondary infections in pneumonia need not result exclusively from the entrance of new germs, but may result also from modification of the primary invader.

The Relationship Between Hormones and Immune Bodies. Yoshitomi Tokumitsu, Beitr. z. path. Anat. u. z. allg. Path. **73**:566, 1925.

The author observed the changes in agglutinating power of the blood produced by injection of endocrine organ extracts in immune animals. Male rabbits were immunized with typhoid bacilli, and the agglutinin titer measured before, and at intervals after, the injection of endocrine substances.

It was found that epinephrin and paratyphoid extract reduced the agglutinin content while thyroid extract increased it. No effect was obtained in experiments in vitro. After removal of the spleen, the changes due to epinephrin and thyroid extract were increased, those due to parathyroid extract were

decreased. Removal of the thyroid lessened the effect of epinephrin and thyroid, not of parathyroid extract. The presence of the parathyroid glands was necessary for the complete effect of all three extracts.

The author concludes that there is a correlation between the suprarenals, thyroid and parathyroids in respect to their influence on the agglutinin titer of immune animals. The presence of the parathyroids is necessary for the reduction of agglutination following injection of epinephrin. The reduction resembles that produced by parathyroid extract, and is a result of overactivity of these glands. The increase after thyroid extract is due partly to hyperfunction of the thyroid itself and partly to hyperfunction of the parathyroids. Therefore it appears that there are two kinds of hyperfunction of the same organ acting antagonistically on the agglutinin titer. The correlation of the different hormones and their composite effect on immune bodies differ according to the given functional conditions, and the hormones of the same gland may, at times, have antagonistic effects.

B. R. Lovett.

Serologic Examination of the Blood of Japanese and Ainus. Y. Ninomiya, Tohuko J. Exper. Med. **6**:266, 1925.

Among the Japanese the blood group containing the largest number of people was found to be group 2 (Jansky), with 39.3 per cent., the next being group 1, with 29.4 per cent. Among the Ainus, a race living in northern Japan, groups 2 and 3 were almost equal, 32.7 per cent. and 34.6 per cent., respectively. Only 19 per cent. of the people belonged to group 1, the smallest percentage in any race yet investigated. In this respect the Ainus differ from all the surrounding races.

B. R. Lovett.

Tumors

Teratoma, Ovarian and Retroperitoneal. Onslow A. Gordon, Surg., Gynec. & Obst. **41**:399, 1925.

In reporting successful removal of a retroperitoneal cystic teratoma weighing 26 pounds, with the patches of bone in its thick walls, Gordon favors the classification now quite general and limits the term dermoid to growths from embryonic epiblastic cells segregated where furrows and clefts are smoothed out by union during development.

Dermoids therefore do not occur in the ovary. Growths so called heretofore are teratomas and arise from all the germinal layers, although structures from the innermost (endoblastic) are least developed and sometimes not found.

The author recommends leaving part of one or both ovaries in removing the cystic teratomas which are usually benign.

The solid ovarian teratomas, of which only about fifty have been reported, on the other hand, grow rapidly and are malignant.

It is assumed that the retroperitoneal teratomas arise from germinal cells left at or near the original site of the ovaries. They are more on the left side and all so far reported are cystic.

Teratomas of the mediastinum and skull have so far proved rather insuperable obstacles to either of the theories for the origin of teratomas, from blastomeres or, at a later period, from germ cells, and this last possibly, as has been suggested, as a consequence of parthenogenesis.

E. R. Le Count.

THE OCCURRENCE OF RETICULUM IN TUMORS. N. C. FOOT and H. A. DAY, Am. J. Path. **1**:431, 1925.

Reticulum is a regular constituent of the stroma of most tumors, except those of the nervous system, and is most abundant in tumors of rapid growth. It is apparently converted into collagen in the more slowly growing neoplasms, does not show any constant relationship to cellular constituents of tumors, but seems to be laid down in continuity with preexisting reticulum in the intercellular fluids or substances by a process independent of cytoplasmic differentiation and analogous to precipitation or crystallization. Silver impregnation of tumor reticulum constitutes a valuable diagnostic method, especially in the case of tumors of endothelial, lymphoid and nervous tissue origin.

MECHANICAL IRRITATION AS ETIOLOGIC FACTOR OF CANCER. NICHOLAS M. ALTER, Am. J. Path. **1**:511, 1925.

A case of carcinoma of the large intestine is described which is interesting because it developed where the head of a polyp had caused long continued friction.

NEUROBLASTOMA OF INTESTINE. SAUL A. RITTER, Am. J. Path. **1**:519, 1925.

Two cases of primary neuroblastoma of the jejunum, apparently the first of their kind, are described in persons past middle age. Probably other instances have been classed as sarcoma. Characteristic rosets were present in one and in the other pyriform cells with a fine fibrillar process coming from the apex. Metastases were present only in the adjacent lymph nodes.

ARGENTAFFINE TUMORS OF APPENDIX AND SMALL INTESTINE. W. D. FORBUS, Bull. Johns Hopkins Hosp. **37**:130, 1925.

A multiplicity of opinions are on record regarding the nature and the origin of the small carcinoid tumors which occur throughout the gastro-intestinal tract. Forbus suggests that the weight of evidence is in favor of the endocrine origin of these tumors and that they may be rightly called "endocrine tumors," or probably better "argentaffine tumors," and permanently separated from the general group of carcinoma. Six cases of so-called "carcinoma" of the appendix and small intestine are described, and the argentaffine or chromaffine character of the cells of these tumors, originally described by Gosset and Masson, confirmed. The "carcinomas" or "carcinoids" of the appendix and small intestine have their origin in the cells of Kultschitsky and Schmidt of the crypts of Lieberkühn and, therefore, are tumors of the chromaffine system. They may be called argentaffine tumors in view of the peculiar ability of the granules of the tumor cells to reduce an ammoniacal solution of silver. The importance of differentiation between the argentaffine tumors and a peculiar form of adenocarcinoma of the appendix and small intestine, which is superficially similar to the argentaffine tumors, is emphasized. Attention is called to the general harmless character of the argentaffine tumors. A review of the literature is given tracing the development of the various opinions regarding the so-called "carcinomas" or "carcinoids" of the gastro-intestinal tract.

CANCER MORTALITY IN THE TEN ORIGINAL REGISTRATION STATES, 1900-1920. J. W. SCHERESCHEWSKY, J. A. M. A. **85**:1175, 1925.

The conclusions are that there has been a pronounced increase in the observed death rate from cancer in persons 40 years and over in that part of the United States known as the ten original registration states. Part of this increase (about 30 per cent.) is regarded as due to greater precision and accuracy in the filling out of death returns. The remainder, however, is believed to be an actual increase in the mortality resulting in a death rate between 25 and 30 per cent. higher than it was twenty-one years ago.

THE RELATION OF THE VITAMINS TO THE REACTION INDUCED BY COAL TAR IN THE TISSUES OF ANIMALS. LOUIS H. JORSTAD, J. Exper. Med. **42**:221, 1925.

Drops of coal tar introduced into the subcutaneous tissue attract the fibroblasts, endothelial and other cells to them. These cells suffer degenerative changes through this action of the tar, and the animal suffers cachectic-like changes and death from large doses of it introduced into the subcutaneous tissue. This action of the coal tar is limited to a short period of time, after which it becomes inert. The cells which have been drawn to it and which have not completely degenerated then slowly recover. When large numbers of these cells are drawn to the tar, they grow and divide after recovering from the initial effects of the tar; cancer may develop. When only a few cells are drawn to the tar, they lay down intercellular fibrils and a scar eventually develops. Vitamin A fed in more than ample quantities to these animals protects the animals and the cells against the toxic action of the tar and stimulates and prolongs their secondary growth. Vitamin B stimulates the secondary growth of these cells. This action is limited in extent and time. It is followed by an early degeneration and hyalinization of the tissue.

AUTHOR'S SUMMARY.

GONGYLONEMA AS CAUSE OF CANCER. L. W. SAMBON, J. Trop. Med. **28**:313, 1925.

The peculiar topographic distribution of cancer in Romagna, the prevalence of the disease in the esophagus and in the cardiac portion of the stomach, the constant presence of cockroaches, meal beetles and cellar beetles — all fosterers of the larval stages of *Gongylonema neoplasticum* in the houses where cancer cases had occurred, led Sambon to wonder whether *Gongylonema* might not be a factor in the causation of certain neoplasms affecting the upper portion of the alimentary tract of man, as is well known to be the case in rats infested by this spiruroid worm.

THE BEHAVIOR OF THE CONNECTIVE TISSUE IN TAR TUMORS OF RABBITS. EDWARD SZCZELIK, Trav. d'Inst. d'anat. path. d. Univ. de Pologne **1**:243, 1925.

The reaction of the connective tissue of tumors due to tar was investigated during their development and regression, and the following conclusions reached:

In the beginning of these tumors in rabbits the connective tissue does not play an active rôle. The later changes in the connective tissue arise under the influence of the growing epithelium, possibly also of the tar, and stand in close relation to the type and the stage of development of the growth.

In the early benign stage, the increase of collagenic and elastic tissue keeps up with the growth of the tumor. In the later malignant stage, the connective tissue undergoes regressive changes, which increase as the tumor develops. As the tumor in turn begins to degenerate, the changes in the epithelium are matched by proliferation of the connective tissue.

The reaction of the wandering cells begins later than that of the connective tissue, increases with the growth of the tumor, and reaches its height in the cancerous stage. It consists in accumulation of pseudo-eosinophils, a few mast and other wandering cells, which invade the epithelium. In the regressive stage, true eosinophils appear.

The changes in connective tissue and wandering cells and the new growth of blood vessels must be regarded as a defense of the organism against the growing epithelium.

XANTHOMATOUS GIANT CELL TUMORS. O. WUSTMANN, Deutsch. Ztschr. f. Chir. **192**:381, 1925.

Wustmann believes that these pathologic products are not true tumors, and certainly not true sarcomas. They are formed to accumulate the excess of cholesterol in these patients. Xanthomatous new growths are strictly dependent on the cholesterol diathesis. They practically never metastasize, and their growth is not infiltrative and destructive.

BONE FORMATION IN DURAL ENDOTHELIOMAS. A. WEISER, Deutsch. Ztschr. f. Chir. **192**:405, 1925.

It is well known that in a considerable percentage of endotheliomas, hyperostoses of the skull are found opposite the tumor. Weiser reports two cases in which he found true bone formation on the cerebral surface of endotheliomas. He believes that this occurrence has never before been described in the literature.

BILATERAL CHROMAFFINOMA OF THE SUPRARENALS. M. BIEBL and P. WICHELS, Virchows Arch. f. path. Anat. **257**:182, 1925.

A man, aged 36, with hypertension, arteriosclerosis and glycosuria, died of hemorrhage into the pons. Each suprarenal was the seat of an adenomatous tumor composed of solid, cord-like alveoli of cells which gave the chromaffin reaction. The authors believe that the hypertension, glycosuria, arteriosclerosis and cerebral hemorrhage were due to an excess of epinephrin formed by the bilateral suprarenal chromaffinomas.

O. T. SCHULTZ.

Medicolegal Pathology

MANIPULATIVE (CHIROPRATIC) DISLOCATION OF THE ATLAS. E. S. BLAINE, J. A. M. A. **85**:1356, 1925.

Cases are reported of dislocation of the atlas by chiropractors in the course of so-called spinal adjustments; also injury to the spinal cord and death in a girl aged 11 from collapse of a tuberculous cervical vertebra during spinal adjustment. Other cases of vetebral fracture or dislocation from spinal manipulations were mentioned in the discussion of Dr. Blaine's paper.

PRESENCE POST-MORTEM OF NITRIC OXID-HEMOGLOBIN. H. A. L. BANHAM, J. S. HALDANE and T. SAVAGE, Brit. M. J. **2**:187, 1925.

The case reported was one in which there is every reason for believing that postmortem appearances which simulated very closely those of carbon monoxid poisoning were due to the formation of nitric oxid hemoglobin after death.

THE CONDITION OF THE SUPRARENALS AND THE SPLEEN IN BURNS, WITH PARTICULAR REFERENCE TO THE CAUSE OF DEATH FROM BURNS AND TO THE CORRELATION BETWEEN THE SUPRARENALS AND THE SKIN. T. NAKATA, Beitr. z. path. Anat. u. z. allg. Path. **73**:439, 1925.

Following the destruction of considerable areas of skin in rabbits and guinea-pigs by the action of hot water or caustic acids or alkalis, the suprarenals enlarge and become hyperemic, areas of hemorrhage and necrosis may be present, and the lipoid content of the cortical cells decreases in amount. These changes are most marked from three to ten days after the burning; they begin to regress before the burn is healed. The alterations noted are ascribed to the action of toxic substances which arise in the burned skin. The action of toxic substances formed in normal metabolism, which should be fixed and rendered harmless by the intact skin, is also held to be a possible cause of the suprarenal changes. In two persons dead of uncomplicated burns, suprarenal changes similar to those in the experimental animals were found. The spleen was found to be slightly hyperemic after the experimental procedures applied.

O. T. SCHULTZ.

THE QUESTION OF OBJECTIVE DETERMINATION OF AGE IN LIVING ADULTS. W. A. NADESHDIN, Deutsch. Ztschr. f. ges. gericht. Med. **6**:121, 1925.

This is an abbreviated account of an inaugural dissertation from the military medical academy at Petrograd in 1922, on a study of 515 men and 490 women, all adults over 20 years. The age estimates are based on tables containing arbitrarily fixed values for the importance of wrinkles at particular places in the skin of the face and neck, for the color of the face and conditions of the teeth.

When these indications of age are present they are given a number from 1 to 4 based on the degree to which they are barely discernible, fairly marked, very marked or fully developed, and by reference to the table, each characteristic is entered in a column by the corresponding age. The ages thus arrived at are then added, the sum divided by the number of characteristics employed, and the quotient obtained is the age. Thus in a given instance in which the nasolabial fold was 1, its age index was 27.5 years according to the table. The suborbital fold 1.5, or 30 years, the eyelid wrinkles 1 equal (referring to the table again) to 31 years, the worn state of the incisor teeth 2 or 32 years, that of the molars 1 or 31 years. The years when added equal 151.5, and this divided by the number of characteristics considered gives the age as 30.3 years or 30 years and between 3 and 4 months. The actual age of the individual so examined was 30 years, 6 months.

Many similar examples are given, and with numerous additional characteristics, each with its age coefficient, as well as descriptions of the alterations produced in these parts of the body by age, and how the values given them in the tables are arrived at. Not all characteristics possess the same value; in fact, the range is considerable, and for women the table employed differs from that for men.

E. R. Le Count.

Investigations in a Case of Adipocere. G. Strassman and Funtl, Deutsch. Ztschr. f. ges. gericht, Med. **6**:168, 1925.

Chemical and microscopic examinations of portions of the adipocere from the headless trunk of the body of a woman removed from the river Elbe demonstrated that the material was chiefly fatty acids and their soaps.

Portions frozen after imbedding in gelatin and hardening the gelatin with liquor formaldehydi yielded sections which stained deep blue with borax-ion ferricyanide after treatment with copperacetate and hematoxylin. This color failed to disappear from the sections treated with hydrochloric acid, excluding potassium carbonate, but did disappear in acidified mixtures of alcohol and ether.

These soaps and fatty acids were tuftlike, colorless and enmeshed in fibers which stained red with van Gieson's stain and with eosin. The fat material also stained deep red with lithium carmine. The usual paraffin-imbedding and removal of the paraffin with xylol was found entirely unsuitable for microscopic study. Brown amorphous masses gave tests for blood pigments microspectroscopically.

The ash was 4.03 per cent., the fat 82.16 per cent., the water 1.22 per cent. and only traces of cholesterol were found.

By saponification of the fats, figures were obtained for the molecular weights of the fatty acids so high that the authors conclude that such results favor the origin of adipocere from the fats normal to the body rather than, as the older view has been, from protein material.

E. R. Le Count.

Technical

An Estimation of the Clinical Value of the Van den Bergh Test. Elizabeth Glenn Ravdin, Am. J. M. Sc. **169**:850, 1925.

Van den Bergh's test for the estimation of the quantity and type of bilirubin in the blood and serum is discussed on the basis of tests on the blood serum of 140 patients. In the cases of common duct stone and of occlusion of duct by tumor or pancreatic disease, there was a strong, immediate direct reaction, with an indirect reading ranging from 1.4 to 18 units. The direct readings from nine patients with chronic cholecystitis were negative or delayed, the indirect reaction being normal in all but one case. Eleven cases of chronic calculus cholecystitis gave indirect readings from 0.2 to 1.9 units. In secondary anemia the indirect results were normal, in pernicious anemia between 0.6 and 4 high (from 1.5 to 4); in leukemia and purpura hemorrhagica the results were negative.

Van den Bergh's test and his interpretation of it as differentiating between the jaundice of obstruction and hemolysis, is in accord with these clinical findings.

J. P. Parsons.

MICROCYTOSIS IN HEMOLYTIC ICTERUS. B. R. WHITCHER, Am. J. Med. Sc. **170**: 678, 1925.

After splenectomy in hemolytic icterus the red corpuscles returned to normal, indicating that the microcytosis is characteristic of the anemia of the disease rather than an inherent peculiarity of the corpuscles of the patient.

CLINICAL AND SEROLOGIC VALUE OF THE COLLOIDAL BENZOIN REACTION. EARL D. OSBORNE, Arch. Dermat. & Syph. **12**:706, 1925.

Judged by the results, the colloidal benzoin test is superior to the colloidal gold test in its ease of performance, uniformity of result, reliability and amount of information furnished. There is a great deal of evidence that precipitation in the first zone is an index of the degree of active involvement of the parenchyma of the brain, and that purely vascular, meningeal or spinal cord lesions produce precipitation in the second zone. Support was not found in this series for the view of Guillain, Laroche and Lechelle that the colloidal benzoin reaction is specific for neurosyphilis in the sense that the spinal fluid Wassermann reaction is. The colloidal benzoin test should have a wide field of usefulness in differentiating general paresis and incipient general paresis from the other forms of neurosyphilis.

AUTHOR'S SUMMARY.

CLINICAL STUDY OF KAHN PRECIPITATION TEST AND KOLMER COMPLEMENT-FIXATION TEST. ROBERT LEE KELLY, Arch. Dermat. & Syph. **12**:720, 1925.

The present study shows a remarkable degree of harmony between the outcome of the Kahn precipitation test and the Kolmer complement-fixation test, and indicates the high degree of sensitivity and specificity common to both. It may not be essential to carry out both tests as a routine, but in doubtful cases both should be performed as they shed a useful complementary light on each other.

Society Transactions

PHILADELPHIA PATHOLOGIC SOCIETY

Oct. 8, 1925

E. B. KRUMBHAAR, *President*

MYCELIAL FILAMENTS IN GIANT CELLS IN LEPROSY. By FRED D. WEIDMAN.

Sections and photomicrographs were shown from the skin of a case of leprosy. The sections presented the unusual feature of filaments inside Langhans giant cells. The latter were numerous, though not many of the filaments were found. These threads were wavy, were several times as thick as lepra bacilli, stained with hematoxylin, and were never segmented. In one instance the thread proved to be acid-fast.

This case was further unusual in the scarcity of lepra bacilli and the rather definite circumscription of the areas of infiltrations.

Similar threadlike structures in other pathologic conditions were demonstrated by lantern slides. These conditions included tuberculosis, blastomycosis, appendicitis and a chronic diffuse granuloma from the leg that histologically bordered on fibrosarcoma. In one of these sections, an intracellular filament was cut in such a favorable plane that its connection could be traced with another filament outside the cell. The latter filament appeared to be an elastic fiber.

The presenter had not satisfied himself whether these threads should be regarded as elastic fibers or as hyphomycetes. If the latter, they might be regarded either as mutants of our better known pathogens (e. g., lepra bacilli as in the case reported) or as new histologic entities. If they are remains of elastic fibers, we would have to recognize that elastic fibers when degenerate may provoke a foreign body giant cell reaction which might easily lead to errors in diagnosis.

BASAL CELL TUMOR OF BREAST OCCURRING IN A CASE OF BASAL CELL CANCER OF FACE. By J. L. GOFORTH.

A white woman, aged 58, entered the Philadelphia General Hospital with an extensive ulcer involving the root of the nose and the left orbit. It had started three years previously as a small "pimple" near the inner canthus of the left eye, had gradually grown larger and often oozed blood. Two years ago the growth was removed by the electric needle, but in six months it recurred, and since then it had slowly grown to its present proportions.

The physical examination was essentially negative, except for the facial condition, and a firm, hen's egg sized, freely movable tumor which occupied the inner upper quadrant of the left breast. This tumor, according to the patient, had been present for at least six years, and had grown slowly. During her four months' stay in the hospital, the breast tumor showed no change. The facial condition grew progressively worse, the patient gradually lost ground, and death followed an intercurrent pulmonary infection.

At necropsy the facial growth had involved all of the root of the nose, the edge of the right eye, and had extended well into the left orbit, completely

destroying the left eye. The rim of the ulcer was firm, rounded, slightly raised and pearly white. There were no enlarged lymph nodes in the neck. The breast tumor measured 6 by 4.5 by 3.5 cm., and the skin over it was intact and freely movable. On section it was solid and appeared cellular, and from gross examination was thought to be an adenofibroma. The lungs showed an early diffuse bronchopneumonia. The other gross anatomic findings were of no consequence.

Microscopically, sections taken from the rim of the ulcer and orbital tissues showed diffuse invasion of strands, sheets and nests of epithelial cells of the basal cell type. Sections from various parts of the tumor showed that it was composed mainly of basal cell proliferations growing in every direction. Little connective tissue was present, and no glandular tissue from the breast was demonstrable in the tumor proper. Study of the cutaneous border showed it to be of normal appearance.

It seems hardly probable that this tumor was a metastasis from the facial growth, although metastasis in basal cell cancer may occur. Finnerud (J. A. M. A. **82:**775 [March 8] 1924) cites two cases of metastasis to the cervical lymph nodes in rodent ulcer of the face and refers to five others in the literature. Ewing (Neoplastic Diseases, Philadelphia, W. B. Saunders Company, **2,** 1922) states that metastasis to the regional lymph nodes may rarely occur in late stages of the disease. It is doubtful, too, whether the tumor was a primary breast tumor. Gross dissection and study seemed to indicate rather that it was a growth in the mammary region, pushing the breast aside. A basal cell tumor could have arisen from an epidermal structure such as a sweat gland, and the easiest explanation of the origin of this tumor is in such an assumption.

EFFECT OF CHICKEN PLASMA AND EXTRACTS ON THE WHITE BLOOD CELLS FROM A CASE OF HUMAN LEUKEMIA. By MAX M. STRUMIA and MORTON MCCUTCHEON. (From the McManes Laboratory of Pathology, University of Pennsylvania Medical School.)

One of the chief difficulties that has beset the cultivation of human tissue in vitro is the tendency of human plasma, used as culture medium, to liquefy. To meet this difficulty, it was proposed by Lambert (1916) to employ a medium consisting of a mixture of chicken plasma and human serum. This author reported that chicken plasma is more resistant to digestion than is human plasma, and allows growth of human tissues.

In the course of a series of experiments with various human tissues in such a mixed medium, we have attempted the cultivation of leukemic blood cells. Such a study should give evidence not only as to the ability of the leukemic cells to multiply in such a medium, but also as to the effect of heterogenic plasma on the locomotion of the leukocytes. The latter point was studied by making control cultures in human plasma. It was also desired to investigate the effect of various extracts, both of the human being and the chick, on migration and on growth.

After twenty-four hours' incubation most of the explants made in human plasma were surrounded by a broad zone of migrated polymorphonuclear leukocytes. The greatest width of this zone was about 3 mm., and was found in the human plasma to which human fetal extracts had been added. However, only slightly less migration occurred in undiluted human plasma. The

only preparations in human plasma in which extensive migration did not occur were those to which chick embryo extract had been added; these showed only a narrow zone of leukocytes.

A striking difference was found in the cultures made with chicken plasma. In none of these did extensive migration occur, and in some there was none at all. Those preparations containing human extracts or serum were only slightly more active than those in pure plasma.

After twenty-four hours the cultures were excised and transplanted. Those previously grown in autogenic plasma were placed in homogenic plasma from a supposedly normal individual, and the same extracts added as before. The leukocytic zone formed by these during the second day was about half as wide as that formed during the first day.

Of the preparations previously in chicken plasma, some were transplanted into the same medium while others were placed in human plasma. These two

Comparative Effect of Human and Chicken Plasma and Extracts on Migration of Polymorphonuclear Leukocytes in a Case of Leukemia

	Human Plasma		Chicken Plasma	
Extracts	Culture No.	Migration	Culture No.	Migration
None	1	+++	14	+
	2	++	15	0
	3	+++	..	..
Chick embryo	4	+	16	0
	5	++	..	..
	6	+	..	..
Human embryo	7	+++	17	+
	8	+++	18	+
	9	+++	19	0
	10	+++	..	..
Adult human muscle	11	++	20	+
	12	+	21	+
	13	++	22	+
Human serum	..	..	23	+
			24	+
			25	++

sets of cultures showed marked differences during the second day. Those transplanted into chicken plasma showed as before little activity, but those placed in human plasma developed marked activity of the leukocytes, the transplants being surrounded by a fairly wide zone of migrated cells.

It is clear from the last mentioned preparations that the chicken plasma had inhibited the locomotion of the leukocytes, without seriously damaging them, for as soon as the cells were removed from the foreign medium and placed in homologous plasma, they displayed normal motility.

POSTMORTEM BLOOD CHEMICAL DETERMINATIONS. By J. R. PAUL. (From the Ayer Clinical Laboratory, Pennsylvania Hospital, Philadelphia.)

Sugar, nonprotein nitrogen, urea nitrogen, creatinin, uric acid, chloride and cell volume determinations were made on a series of samples of blood taken after death and under certain specified conditions.

By collecting samples from a cadaver immediately after death and again at the end of twenty-four hours, it was found that one may estimate the degree of postmortem fluctuation which these constituents of the blood usually undergo.

In a series of nine cases from which at least two samples of blood were analyzed at stated intervals, it was found that during the first twenty-four hours after death the blood sugar rapidly falls to insignificant values, the nonprotein nitrogen rises, the urea nitrogen and creatinin remain fairly stationary, and the uric acid and chloride content seems to fluctuate irregularly, as does also the ratio of cells to plasma volume.

As a result of this work, it was concluded that in spite of the great number of complicating and variable factors which confuse the results of postmortem blood chemical studies, valuable information may be gained from some of them. This is particularly true in the case of blood urea nitrogen and creatinin determinations, provided certain precautions are taken. With these determinations an index of terminal renal function may be obtained which is useful to the pathologist in his attempt to place a renal lesion in the anatomic diagnosis in its proper chronologic order, particularly if clinical data on the case happen to be lacking.

ADVANTAGE OF UTILIZING INHIBITORY INFLUENCE OF WHOLE BLOOD IN ACCENTUATING SPECIFICALLY PATHOGENIC ORGANISMS IN CULTURES. By MYER SOLIS-COHEN.

The ordinary culture fails to differentiate between organisms that are pathogenic for the patient, and hence infecting him, and those that are nonpathogenic for him, of which he is merely a carrier. The organism that predominates in such a culture frequently has little or no pathogenicity for the host, and therefore cannot be regarded as of etiologic significance. On the other hand, an organism which is the etiologic factor, even when planted on a suitable culture medium, may be missed through having its growth inhibited by organisms that are nonpathogenic for the patient and asymbiotic. Vaccine prepared in the usual manner may therefore contain little or none of the required antigen.

The patient's fresh, whole, coagulable blood, which is believed to possess bactericidal or bacteriostatic power against organisms that are nonpathogenic for him and to lack it against organisms that are pathogenic for him, furnishes a means of separating organisms that are infecting or capable of infecting, him from those of which he is merely a resistant carrier. When cultures from body recesses, fluids and excretions are made in vitro in the patient's whole coagulable blood, the growth of organisms regarded as pathogenic for him is promoted and accentuated, while the growth of those regarded as nonpathogenic for him is inhibited or completely checked.

There are two methods. In the capillary-tube (Heist-Lacy) method, an undiluted culture of each organism tested is run in and out of one capillary tube, and each of five dilutions of the culture, each being one-tenth the strength of the preceding one, is similarly run in and out of one of five other capillary tubes. The tubes are then filled with the patient's fresh, whole blood, incubated for twenty-four hours and then broken, the contained blood being stained and examined for the presence of bacteria.

In the more desirable test-tube, or pathogen-selective, method, the applicator, after being applied to the part or substance to be cultured, is stroked over a rich culture medium and then rubbed on the inside of a sterile empty test-tube, which is immediately filled with the patient's fresh whole blood. Both tubes are incubated for twenty-four hours, the plain tube then being placed in an ice-box to prevent further development. The clotted blood is removed from

the other tube, and with a sterile platinum loop the residual blood at the bottom of the tube is inoculated on one or more tubes of plain culture medium in a thin film on the surface and incubated for twenty-four hours.

At the end of this period the plain cultures previously placed in the ice-box and those inoculated from the blood tubes are examined for organisms, the amount of growth of each being noted.

The whole blood, by restraining organisms that are nonpathogenic for the patient, permits a relatively free growth and multiplication of the organisms that are pathogenic for the patient, even if on the smears from the plain culture they were proportionately few in number.

THE FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY

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The Society for Experimental Pathology

SYPHILITIC MYOCARDITIS IN THE RABBIT. By WADE H. BROWN and LOUISE PEARCE.

In the course of routine postmortem examination of rabbits infected with *Spirochaeta pallida,* six cases of pronounced granulomatous myocarditis were encountered. Spirochetes were not demonstrated in the lesions, but the clinical history and the gross and microscopic appearance of the lesions seemed to warrant a diagnosis of syphilitic myocarditis. The lesions measured 1 cm. or more in diameter and histologically were practically identical with those described by Warthin in cases of syphilitic myocarditis in man.

These are the first cases of syphilitic myocarditis or of visceral syphilis in the rabbit that have been reported.

DISCUSSION

DR. WARTHIN: I look with a great deal of suspicion on all rabbit experiments with regard to pathologic changes. Lesions of all variety occur in so-called normal rabbits, and no spirochetes have been demonstrated in the lesions obtained in these experiments.

DR. HAYTHORN: Was injection of the tissues made into normal animals?

DR. BROWN: Replying to Dr. Foot's inquiry about the coronary arteries, I agree with Dr. Warthin, but I never saw *such* changes in normal animals. I have observed nothing in the vessels, and we do not attempt to inject the tissues into normal animals to obtain the organism, because during active syphilis the blood carries the organism.

EFFECTS OF THYROIDECTOMY AND OF THYMECTOMY IN EXPERIMENTAL SYPHILIS. By LOUISE PEARCE and C. M. VAN ALLEN.

The effect of complete and of partial thyroidectomy and of complete thymectomy in experimental syphilis was studied in rabbits inoculated shortly after operation. Complete thyroidectomy resulted in a disease that was more

severe than that of the controls, particularly as regards the primary and metastatic orchitis, and in most animals in the number of generalized manifestations, while there was a noticeable tendency toward an unusual persistence of all lesions. Partial thyroidectomy, on the other hand, resulted in a milder disease than that of the controls. The disease which developed in completely thymectomized rabbits resembled, on the whole, that of partially thyroidectomized rabbits.

We have interpreted the effects of these operative procedures on the basis of the host's reaction and resistance to experimental syphilis and have concluded that the integrity and balance of the system of glands of internal secretion play an important part in the mechanism of defense against this infection.

THE ATTEMPTS TO PRODUCE AN EXPERIMENTAL PERNICIOUS ANEMIA BY MEANS OF MONILIA PSILOSIS. By ALDRED SCOTT WARTHIN.

It has been claimed by a number of tropical observers that there is a strong similarity between sprue and pernicious anemia and that the organism, *Monilia psilosis,* may be responsible for both conditions. Wood has claimed that he has been able to produce experimentally the picture of pernicious anemia in rabbits by injections of filtrates and cultures of *Monilia psilosis.* This paper gives an account of the control of Wood's experiment on the use of three different strains of *Monilia psilosis,* with negative results in all cases.

DISCUSSION

DR. ROSENOW: Organisms kept under artificial conditions rapidly undergo changes, deterioration, and this may account for failure.

DR. BROWN: Climatic conditions may account for difference.

DR. WARTHIN: One strain was virulent and obtained from a returned missionary. The other two were stock strains. Little can be said regarding climatic conditions.

EXPERIMENTAL OBSTRUCTION OF SECRETION FROM THE PARS NERVOSA. By H. CUSHING and S. J. MADDOCK.

The hypophysial stock of dogs was clamped with a clip—a bloodless operation. In a day or two the posterior lobe became filled with pink staining homogeneous material. The cells proliferated, took on a hyaline appearance, and cyst formation occurred later (thirty days). There was also hypertrophy of the pars intermedia. The authors believe that secretion continues and accumulates behind the clamped stock. The dog clinically showed diabetes

DISCUSSION

DR. IVY: Was not the colloidal the result of degeneration?

DR. KRUMBHAAR: If this conclusion of the experiment is valid, it raises the question whether the tuber cinereum plays any rôle in the production of diabetes insipidus.

DR. CUSHING: I think that the blood supply was intact, hence the colloid was not the result of degeneration.

TEMPERATURE CHANGES IN DOGS FOLLOWING EXCESSIVE ADMINISTRATION OF WATER. By C. H. GREENE and L. G. ROWNTREE.

Water has been administered in excess to dogs by the method formerly reported in the authors' work on water intoxication. Automatic rectal temperature records were taken, utilizing the tag recorder of Tagliaboo. The room temperature in the various experiments varied from 19 to 24 C. Water at

various temperatures from 0 to 50 C. were administered. Their experiments showed that an excessive ingestion of water tends to decrease body temperature.

With cold water this is striking, amounting to as much as 6 to 7 F. With water at body temperature or even at 50 C., there is still a slight but definite decrease in body temperature.

FOWL PARALYSIS: PATHOLOGY AND ATTEMPTS AT TRANSMISSIONS. By ALVIN M. PAPPENHEIMER, WILLIAM V. CONE and LESLIE C. DUNN.

In the condition known to poulty-men as "fowl paralysis," lesions are present in all parts of the nervous system. Most characteristically and intensely affected are the peripheral nerves, dorsal ganglions and nerve roots, which are the seat of an infiltration of mononuclear cells, small lymphoid cells, large mononuclear and plasma cells. Degenerative changes in the nerve fibers (demyelinization, swelling of axis cylinders, presence of fatty granule cells) occur in the later stages.

The lesions of the brain and cord are predominantly focal and perivascular in distribution, consisting of mononuclear cell accumulation in and about the arterioles and capillaries. No parasites could be demonstrated in these lesions. In a small number of birds, a cellular infiltration of the iris, with blindness, was present.

Lesions of similar character, but rarely affecting the peripheral nerves, were found in a large proportion of apparently normal chickens showing no clinical symptoms of paralysis.

In a certain proportion of the birds examined, lymphomatous visceral tumors or microscopic lymphoid infiltrations were associated. None of the chickens, however, were leukemic.

Experiments designed to determine the transmissibility of the disease have not as yet led to positive conclusions. Twenty-one young adult chickens have been inoculated with (*a*) a saline suspension of brain or cord; (*b*) Berkefeld N filtrate of ground brain; (*c*) glycerinated brain and cord. The material was usually injected directly into the brain; a few birds received intravenous or subcutaneous injections. Sixteen of twenty birds on histologic examination showed more or less characteristic lesions of the brain and cord; infiltrations of the peripheral nerves were found in approximately 50 per cent, as compared with about 7 per cent in the apparently normal controls. Only one of the inoculated chickens developed a fatal paralysis; some of the birds showed transient incoordination and tremors of the legs; the majority remained free from symptoms. In view of the occurrence of lesions in a high percentage of nonparalyzed birds, it is thus not justifiable to draw positive conclusions as to transmissibility from these experiments.

Six 10 day old chicks were inoculated subdurally with brain suspension from a typical case of paralysis. Five of them killed at various intervals showed lesions of the nervous system; the sixth is now partially paralyzed in both legs, but has not yet been studied anatomically. Controls of parallel age from the same hatchings have with one exception been free from lesions. Further experiments with young chicks are in progress.

DISCUSSION

DR. WARTHIN: I think that the condition was similar to fowl leukemia. I should like to know about the blood counts.

DR. PAPPENHEIMER: In the entire literature of fowl leukemia nothing is found concerning changes in the nervous system. We looked for leukemic changes in the blood of the birds. The birds were not leukemic because the blood picture was normal.

THE PERSISTENCE OF THE GLOMERULAR CIRCULATION OF THE KIDNEY FOLLOWING OCCLUSION OF THE RENAL VEIN OF ONE KIDNEY IN THE CAT. By ISOLDE T. ZECKWER.

With a view to determining experimentally whether any characteristic changes followed venous obstruction of the kidney, the left renal vein in a series of cats was cut between ligatures, and the animals were killed at varying intervals of time. The resulting changes were found to present an unexpected picture which seemed to furnish data on the finer circulation of the kidney not furnished by other experimental methods.

The distinctive feature of the picture following venous obstruction is the preservation of glomeruli in contrast to the widespread destruction of tubules. The early changes of congestion and edema are followed by degeneration and necrosis of tubules, most marked in the periphery of the cortex. Later all tubules are completely destroyed and replaced by connective tissue, while glomeruli are preserved, so that at the end of the second month, the atrophied kidney consists microscopically almost wholly of closely approximated glomeruli.

Injections of Berlin blue solution through the renal artery of these atrophied kidneys show a free circulation through the glomeruli, and the path of the circulation can be traced in microscopic sections through the kidney from the main renal artery, through efferent vessels to the glomeruli, then through postglomerular vessels to preexisting extrarenal anastomosing channels. This collateral circulation involves only the glomeruli and excludes the tubules. There is then a certain independence of the vascular supply of the glomeruli from that of the tubules.

RADIATION STUDIES IN BIOLOGY (RADIOCHEMICAL INACTIVATION OF ENZYMES). By RAYMOND G. HUSSEY.

Some time ago in collaboration with Mr. W. R. Thompson, Dr. Hussey commenced an investigation of the effect of radioactive radiations, roentgen rays, and ultraviolet radiation on enzymes in solution. Some of the results of this work have been published in the *Journal of General Physiology*.

In their first experiments dilute solutions of trypsin were irradiated and it was found that definite inactivation of the enzyme resulted. Furthermore, it was found that it is the active or dissociated enzyme that is affected, and in following the course of this radiochemical change it was found that the rate of change in the logarithm of the concentration of active enzyme is proportional to the power of the radioactive source. The form of the curve describing the course of the inactivation is the same as that found for mononuclear chemical change. The active enzyme concentration was determined by Northrop's viscosity method.

Following these observations, the effect of the same radiations on pepsin and invertase was studied. Both of these enzymes are inactivated by the radiations under discussion, and the principles involved in the radiochemical reactions studied are apparently the same. In the case of pepsin it was also observed that variation in temperature is associated with only slight variation in the speed of the radiochemical inactivation. Furthermore, evidence has been adduced which indicates that the effect of gamma radiation is negligible with respect to that of beta radiation on pepsin in solution.

When pepsin is irradiated with the radiations from a mercury arc in quartz, under proper experimental conditions, the active enzyme is inactivated and the form of the curve of inactivation is also similar to that of monomolecular chemical change. When trypsin in solution is irradiated by roentgen rays of

relatively long wave length, definite inactivation is effected, but we were unable to measure any change effected in solutions of trypsin by shorter wave length roentgen rays or to study the kinetics of the radiochemical inactivation of trypsin effected by the long wave length roentgen rays.

STUDIES ON COMPENSATORY HYPERTROPHY OF THE CORTEX AND MEDULLA OF THE SUPRARENAL GLAND. By DAVID P. SEECOF.

Adult cats and rabbits were used to determine whether the medulla as well as the cortex participates in the enlargement due to compensatory hypertrophy. The method consisted of removing the left suprarenal gland, allowing an interval of four weeks for hypertrophy, and then estimating the volumes of cortex and medulla by measuring their respective areas in sections taken through the middle of the glands. The data show that in both the cat and the rabbit removal of one suprarenal results in gross enlargement of the remaining gland, which, so far as the method used permitted Dr. Seecof to draw conclusions, seemed limited to the cortex. The medulla may even be reduced in volume.

ANAPHYLACTIC SHOCK CAUSED BY ANTIBODY IN ANIMALS SENSITIZED BY ANTIGEN. REVERSED PASSIVE ANAPHYLAXIS. By EUGENE L. OPIE and J. FURTH.

Having previously found that the Arthus phenomenon may be reversed, experiments have been undertaken in young rabbits to determine whether the meeting of antigen and antibody is sufficient to produce anaphylactic shock irrespective of the order of their introduction into the body. The experiments showed that anaphylactic shock occurs when the usual procedure employed for passive sensitization is reversed. In rabbits which have received antigen the corresponding antiserum in sufficient quantity causes anaphylactic shock and death. The reaction occurs under conditions which reproduce those of passive anaphylaxis. An interval of approximately four hours must intervene between the injection of antigen and injection of antiserum. Animals sensitized to horse serum may be desensitized by repeated injection of antihorse serum in a quantity insufficient to cause symptoms. Anaphylactic shock, like the specific inflammatory reaction of the immunized animal or Arthus phenomenon, occurs when antigen and antibody meet, and in either instance the usual order of their introduction may be reversed, but in the former instance they meet within the tissue spaces, whereas, in the latter contact occurs by way of the circulating blood. Evidence favors the idea that phenomena of anaphylaxis are referable to changes within the cells. Local anaphylaxis occurs under conditions identical with those which induce general anaphylaxis, except that in the first instance antigen and antibody are brought together within the tissue spaces outside of blood vessels and cause inflammation, whereas in the latter one or the other of the two agents is introduced by the circulating blood and has the opportunity of coming into contact with those tissues which after preparation by the other agent are most susceptible to the two in combination. We believe that the precipitate formed by precipitin and precipitinogen may be at the base of the reaction and that it is unnecessary to assume the explosive formation of a toxic substance.

THE SPLANCHNOPERIPHERAL AUTONOMIC BALANCE. By W. F. PETERSEN and E. F. MÜLLER.

Blood pressure is maintained at a relatively constant level by means of an antagonistic orientation of autonomic impulses of the splanchnic and peripheral areas. Müller's previous work has made it probable that a similar balance controls the distribution of the leukocytes.

We have studied the splanchnoperipheral balance in dogs with thoracic duct in cannulation. Operative manipulations were made with local anesthesia, and the animals were in normal condition, resting quietly. Previous work has made it probable that a splanchnic parasympathetic overbalance becomes manifest in the lymph with a lowering of the sugar, increase in protein, calcium and occasionally bile pigment; sympathetic overbalance, on the other hand, with increased lymph sugar, diminished calcium and protein. The peripheral status can be determined by the leukocyte count. Leukopenia is associated with the sympathetic leukocytosis with the parasympathetic overbalance.

Normal balance was disturbed by two methods. Eye pressure was made in one series. Response varied. The vagus effect on the heart was always obtained. The splanchnic effect might be an immediate sympathetic or a parasympathetic effect. The peripheral orientation was almost always the reverse of the splanchnic. Usually the response was a wavelike series of alternating sympathetic and parasympathetic effects.

In a series of experiments carried out with von Oettingen in which the skin of the abdomen was irradiated with ultraviolet light, a similar result was obtained. Occasionally the wavelike response was of increasing amplitude.

The continuous observations make apparent the fallacy of deductions from occasional observations in determinations of alterations of changes in the autonomic nervous system. With disturbances, a series of wavelike alterations in tonus occur, at times of increasing amplitude. With eye pressure the typical vagus heart effect may be associated with a sympathetic splanchnic effect. The fluctuations probably represent efforts at restitution to the normal.

DISCUSSION

DR. STEINBERG: Where was the lymph obtained?

DR. KARSNER: I welcome the data. With the improved method of Moritz on the determination of colloidal calcium important data may be added to the work.

DR. BROWN: This work may be related to many functional manifestations.

DR. PETERSEN: We used thoracic incannulations. The experiment was not complicated.

THE RELATION OF THE THYROID GLAND TO ANAPHYLACTIC SHOCK. By MOYER S. FLEISHER and C. M. WILHELMY.

Kepinow and Lanzenberg claim to have shown that thyroidectomy inhibits the occurrence of anaphylactic shock in both guinea-pigs and rabbits, and further believe that thyroidectomy interferes with the sensitization of the animals.

It was found by Fleisher and Wilhelmy that of fifty-three thyroidectomized guinea-pigs eighteen showed typical fatal anaphylactic shock, whereas twenty-four of thirty-one normal sensitized control animals died. In rabbits that have been operated on, however, no evidence of protection from anaphylactic shock was noted, but there appeared in the thyroidectomized shocked animals an asthenic condition rather different from the reaction seen in normal shocked rabbits. We were able to produce passive sensitization as readily with the blood of thyroidectomized sensitized rabbits as with the blood of normal sensitized animals. We believe that the influence of thyroidectomy on anaphylaxis is to change the physiologic reactions at the time of shock rather than the functions concerned with response to the first injection of antigen. The quantitative physiologic

phenomena attending shock are different in the rabbit and guinea-pig, so the relation of thyroidectomy to the manifestations of shock may well differ in the two species.

Further support to the concept that the response of the thyroidectomized animal to the second injection is changed, is brought out by studies of the surface tension of the plasma. While following an injection of antigen in normal shocked animals there appeared an average fall of surface tension of 1.82 dynes and in normal nonsensitized animals a rise of 2.25 dynes; in the thyroidectomized sensitized animals there was an average fall of only 0.55 dynes.

DISCUSSION

DR. ECKER: Thyroidectomy in the rabbit always means partial parathyroidectomy. Have Drs. Fleisher and Wilhelmy considered the factor of partial parathyroid extirpation? Further anaphylaxis is an individual question varying tremendously from animal to animal. Did the authors make records of blood pressure, respiration, etc., of their rabbits?

DR. MARINE: What is the time relationship between sensitizing and toxic doses?

DR. FLEISHER: The measure is death. I cannot tell very much regarding the parathyroid. The time relationship was regularly greater than fourteen days.

EFFECT OF SOLUBLE TOXIC SUBSTANCES OF B. PARATYPHOSUS B ON INTESTINAL MOTILITY. By E. E. ECKER and A. RADEMAEKERS.

It was shown by Ecker and others that rabbits receiving intravenous injections with 2 to 5 cc. of a Berkefeld filtrate of young cultures of organisms of the paratyphoid-enteritidis group became weak, prostrated and dyspneic in from one to two hours. The animals often suffered from a profuse diarrhea. Control animals receiving broth alone never reacted. An attempt was made to study the action of these toxic filtrates on the intestinal movements, because of little exisiting knowledge. The longitudinal musculature of the upper intestines was studied by the pouch method of Sollmann. The rabbits were kept under urethane, and broth and toxin were given by vein. To determine the effect of broth a series of animals first received injections with sterile broth. An immediate slight rise of tone was observed which returned to normal within from three to five minutes. The toxin broth, however, following the same immediate broth effect, produced a marked rise in tone, reaching a maximum in one series of experiments in twenty-five minutes and in another in fifty-eight minutes. In the first series no preliminary sterile broth injection was given. In the first series the diastolic rise was from 13 mm. to 80 mm.; the systolic was from 42 to 110 mm. In the second the diastolic rise was from an initial drop to —5 mm. to 53 mm. and the systolic from 5 mm. to 70 mm. At least ten to twenty minutes elapsed before the rise was distinct. The rise was persistent and magnesium sulphate or chloride (isotonic) relaxed the muscle again. The circular coat and propulsive efficiency was then studied by the Sollmann and Rademaekers modification of the Max Bauer technic. With this more complicated arrangement the output was markedly increased following intoxication of the animal. Experiments on the isolated segment (Magnus method) failed, and so far nothing can be said as to whether or not the reaction is peripheral. Antiserums protected against the toxic effects (same arrangements) while normal serums failed.

DISCUSSION

DR. HAYTHORN: Dr. Menten studied the pathologic changes produced by these substances in the rabbit. A rise of blood sugar was noted. Was there an increased absorption?

DR. MENTEN: Are the substances true toxins? I have not observed the common occurrence of diarrhea.

DR. ECKER: There was considerable congestion of the mucosa with a possible increase of absorption. The toxins have all the earmarks of stimulating antibody formation. Variations were observed in the different strains with regard to production of diarrhea.

SUPRARENALECTOMY AND SUSCEPTIBILITY TO TETANUS TOXIN. By J. M. ROGOFF and E. E. ECKER.

The influence of suprarenalectomy on the susceptibility to tetanus toxin was investigated in white rats.

Eighty-one rats that had been operated on were used. In sixty of these bilateral extirpation of the glands was complete, and careful macroscopic search at necropsy failed to reveal the presence of accessory suprarenal tissue. In the remaining twenty-one rats, either partial suprarenalectomy was purposely performed for control, or accessory suprarenal tissue was found postmortem.

Thirty-three unoperated rats were used to determine the minimum lethal dose of the toxin. These rats were kept in individual cases, under the same conditions as the rats that had been operated on.

To eliminate any possible personal factors, all suprarenalectomies were performed by one of us (R), and the toxin injections by the other (E), each keeping separate notes on his part of the investigation until the experiments were entirely completed.

The toxin employed was a dry, powdered preparation, kept for about a year in the refrigerator and administered in saline solution. Its toxic capacity was titrated in January and again in June, when the present series of experiments was begun. No change of toxicity was found. It was injected intramuscularly into the left hind leg.

The rats that had been operated on received injections with the toxin from four to twenty-eight days following the excision of the suprarenals. Doses administered ranged from one-fifth up to the full minimum lethal dose.

No difference could be demonstrated between suprarenalectomized (complete or partial) and unoperated rats in susceptibility to tetanus toxin. Local tetanus appeared in both sets of animals after about the same period, and tolerance to given doses was the same.

THE EFFECT OF ANTISERUM AGAINST THE SOLUBLE TOXIC SUBSTANCE OF B. COLI IN B. COLI PERITONITIS. By BERNHARD STEINBERG and E. E. ECKER.

Colon bacilli were injected into the peritoneal cavity of rabbits, and the animals died within a few hours. There was an incubation period of from one to one and a half hours, which was followed by a set of symptoms that culminated in death.

It was thought that the soluble toxic substance produced by young cultures of *B. coli* was an important lethal factor. Young cultures of *B. coli* (eighteen of twenty-four hours) in broth were centrifugalized, and after killing the remaining bacteria by heat the supernatant fluid was injected into the peritoneal

cavity of rabbits. The same set of symptoms terminating in death which was seen on the injection of the whole culture resulted when the supernatant fluid alone was given.

An antiserum against the soluble toxic substance of *B. coli* was produced in rabbits by weekly intravenous injections for six weeks.

When this antiserum was given intravenously to twelve rabbits immediately or one-half hour after receiving intraperitoneally five times the usual lethal dose of *B. coli*, ten of them survived. Normal and agglutinating serums failed to protect.

DISCUSSION

DR. ECKER: On the basis of results I obtained with other members of the colon-typhoid group I believe that the idea that an immune serum can be produced against these soluble toxic substances is becoming evident. Protection was definite in these experiments.

DR. HARTMAN: I should like to know about the rôle of bacteriolysin.

DR. ECKER: Serums of animals immunized with washed bacteria failed to protect. The latter serums had a high agglutinating power, but no determinations were made of the lysin.

DR. KARSNER: The time is approaching when we can speak of an exotoxin in this group of organisms. How much of a part septicemia plays in peritonitis is difficult to state. In the rats, peritonitis was definite, and all the animals survived when the antiserum was given.

THE PRODUCTION OF PULMONARY EMBOLI IN SUPRARENAL INSUFFICIENCY. By W. J. M. SCOTT and H. S. THATCHER.

A search for histologic changes was made after the employment of agents which, by their effect, differentiate suprarenalectomized rats from operated control animals. Egg albumin was injected intravenously into seventeen doubly suprarenalectomized rats and into thirteen singly suprarenalectomized rats. In 53 per cent of the former, smaller pulmonary vessels, both arterioles and venules, were found plugged with large mononuclear cells. This phenomenon was not observed in the operated controls (except in one instance complicated by an abdominal abscess), nor in doubly suprarenalectomized animals receiving intravenous injections with saline. Such cellular plugs were seen in suprarenalectomized rats dying from the repeated injection of bacterial vaccine, and from suprarenal insufficiency.

DISCUSSION

DR. ECKER: What is the effect of egg albumin on the corpuscles of the rat, and what is the relation of possible infection and thrombus formation?

DR. MARINE: Are the cells leukocytes or endothelial cells? Marked stimulation of lymphoid tissue follows suprarenalectomy.

DR. KARSNER: The phenomenon may be one of colloid shock and not directly a question of increased susceptibility of the animals.

DR. BROWN: At present it is most desirable to accumulate facts and to leave explanations for a later date.

DR. SCOTT: I cannot answer the questions asked by Dr. Ecker. Although monocytes may be found in large numbers following repeated injections of a colloid into normal animals, suprarenalectomized animals show the shower phenomenon after a single dose of the colloid.

CALCIFICATION OF THE SUPRARENAL GLANDS IN CATS. By DAVID MARINE.

In the routine gross and histologic examination of the tissues of 245 cats, calcification of the cortical portion of the suprarenal glands was found in fifty-nine instances, or 24.5 per cent. It usually, if not always, occurs in association with distemper, and is more common in young cats. Other types of injury, as by freezing, diphtheria toxin and arsenic, are not followed by calcification. Much larger series of suprarenal glands from pigs, cattle, sheep, dogs and rabbits have been studied, but no instance of calcification of this type has been seen. The condition may be suspected clinically. Deposition of calcium usually begins in the fascicular zone, probably in the form of soaps, which later changes to carbonate.

DISCUSSION

DR. ROSENOW: I noted the absence of cellular infiltrations.

DR. BROWN: Were there comparable lesions elsewhere?

DR. MARINE: Little infiltration occurs around tissues rich in lipoid. Lipoidal substances prevent absorption. I have not noticed the same phenomena in other tissues.

STUDIES IN THE INTRAHEPATIC VASCULAR AND BILIARY TREES. By ARCHIBALD H. MCINDOE and VIRGIL S. COUNSELLOR.

By means of a modified celloidin injection and corrosion specimen technic, the effect of cirrhosis on the vascular tree and of lesions of the biliary apparatus on the biliary tree has been observed. For the sake of comparison a large number of normal livers were first injected in various combinations of vessels. In marked portal cirrhosis the disturbance was mainly in the smaller branches of the portal and hepatic veins, with the development of the collateral circulation on the portal side. Strangulation and obliteration of veins was the important factor in the development of permanent ascites.

The various grades of biliary obstruction, from partial to complete, were shown to produce dilatation of the ducts to enormous proportions, resembling the condition seen in hydronephrosis and bronchiectasis. The dilatation extends to the finest interlobular bile ducts, and in prolonged obstruction a verrucose condition of the ducts is produced. In functionless gallbladders and in old cases of cholecystectomy mild dilatation of the extrahepatic bile passages occurred without any increase in size of the parietal sacculi or vasa aberrantia.

DISCUSSION

DR. MCINDOE: In response to the question whether a study was made in case of marked long-standing passive congestion: A case of marked passive congestion in a child with congenital heart defect was studied.

EXPERIMENTAL NEPHRITIS PRODUCED BY IRRITATION. By F. W. HARTMAN.

Dogs were selected that showed no functional evidence of kidney injury. They were then divided into two groups. From the first group one kidney was excised for study before irradiation. In the second group both kidney areas were irradiated. Single or repeated exposures over the kidney areas were administered with the deep roentgen ray, sufficient to produce skin reactions from falling of the hair to deep ulceration.

During the first month after irradiation the signs of renal damage were principally albuminuria and polyuria. In most instances the dogs were kept

until they died, periods ranging from two to thirteen months. The period just before death was accompanied by nitrogen retention, low dye excretion, elevated blood pressure, loss of appetite, vomiting, coma and nuria.

The pathologic changes are essentially those described under the name chronic diffuse nephritis, and in some cases were complicated by an acute suppurative nephritis.

DISCUSSION

DR. WARTHIN: Are there any deposits of lime salts? Calcification may follow roentgen-ray application.

DR. WHIPPLE: May not Dr. Hartman have included coils of intestines in his irradiation experiments? Intestinal epithelium is sensitive to the rays, and perforation may occur.

DR. HARTMAN: Chalk was deposited in one case and was scattered through the medullary portion. I also noticed injury of the intestines in these experiments but no perforation.

A METHOD FOR THE EXPERIMENTAL PRODUCTION OF LUNG ABSCESS. By S. A. SCHLUETER and I. F. WEIDLEIN.

An experimental procedure for the production of lung abscess has been developed in which the infective element is permitted to reach the lung tissues via the blood stream in the form of a septic embolus instead of by way of the bronchi. A segment of femoral vein, tied at both ends, encases the organisms, a drop of blood and a bit of lead filing. This septic embolus is introduced into the jugular vein of a dog. The lead filing is added so that the exact location of the embolus can immediately be ascertained by roentgenograms. The method has proved successful in 75 per cent of the experiments.

DISCUSSION

DR. HAYTHORN: Were the same organisms later recovered from the abscess, and no others?

DR. SCHLUETER: Such was the case.

THE USE OF ZINC SALTS IN THE DIFFERENTIATION OF HEMOLYTIC STREPTOCOCCI. By R. C. AVERY.

As previously reported, definite concentrations of a methylene blue serve to distinguish two large groups of hemolytic streptococci. The group which was more sensitive to the dye comprised strains which had been isolated from infectious processes of man and cattle; the second or methylene-blue-tolerant group includes strains which are commonly present in dairy products, but which, so far as known, are not associated with infection.

In this paper it is shown that the addition of zinc sulphate to agar in a concentration of 1:5,000 differentiates the same two groups of hemolytic streptococci which were distinguished by methylene blue. The bacteriostatic action of methylene blue, however, cannot be explained by the traces of zinc frequently present in the medicinal dye, since the dye suffers no loss in activity after removal of all traces of zinc by chemical purification.

The differentiation by zinc salts would appear to be based on fundamental differences among hemolytic streptococci, since the presence or absence of growth on zinc sulphate agar can be correlated with other biologic characters: differences in colony structure, in morphology, diffuse and granular growth in broth, high and low acid production, and fermentation reactions.

BEHAVIOR OF VITAL DYES IN THE CIRCULATION. By H. P. SMITH.

Brilliant vital red and Niagara sky blue were used. The absorption of brilliant vital red is greatest at the green-blue end of the spectrum and that of Niagara sky blue greatest at the red end of the spectrum. Rapid elimination occurs during the first six hours following their administration. Some Niagara sky blue remains in circulation at the end of twenty-four hours. An animal stained with the red dye may eliminate the blue dye rapidly. The intense staining of animal tissues with a dye will not cause inhibition of the tissue to take up another dye. On histologic examination of the tissues both dye granules may be found.

DISCUSSION

DR. HAYTHORN: Did the endothelial linings in the lung take up the dye? What is the technic of preparing the tissue for examination?

DR. MACCALLUM: It looked as if there were no blocking.

DR. KRUMBHAAR: What quantities were injected? What is the toxicity of the dyes? Was the retina examined?

DR. SMITH: The capillaries of the lung were less intensely stained. The dyes are soluable in alcohol and water, and frozen sections were made. According to the author, not more than 20 per cent of the dye was taken care of by the liver in twenty-four hours. He used 2 per cent suspensions, and 15 cc. were injected into a 30 pound (13.6 Kg.) dog. Daily for eight days 20 cc. were given. If longer continued, the animals become intoxicated. The suprarenals and bone marrow took up the dyes. The retina was not examined.

STUDIES IN EXPERIMENTAL ATHEROSCLEROSIS IN RABBITS. By SHEPARD SHAPIRO.

Atheromas of the aorta were produced by feeding 4 Gm. of hydrous wool fat in cottonseed oil daily to: (1) normal rabbits, (2) gonadectomized rabbits, (3) splenectomized rabbits, (4) suprarenalectomized rabbits and (5) thyroidectomized rabbits. It was found that thyroidectomized rabbits were most susceptible, splenectomized rabbits next and gonadectomized rabbits third, as compared with rabbits with all organs intact. The suprarenalectomized rabbits were least susceptible of the operated animals.

TEMPERATURE CHANGES IN DOGS FOLLOWING EXCESSIVE ADMINISTRATION OF WATER. By C. H. GREENE and L. G. ROWNTREE.

Water has been administered in excess to dogs by the methods formerly reported in our work on water intoxication. Automatic rectal temperature records were taken, utilizing the tag recorder of Tagliaboo. The room temperature in the various experiments varied from 19 to 24 C. Water at various temperatures from 0 to 50 C. was administered. The experiments showed that an excessive ingestion of water tends to decrease body temperature.

With cold water this is striking, amounting to as much as 6 to 7 F. With water at body temperature or even at 50 C., there is still a slight but definite decrease in body temperature.

EFFECTS OBTAINED FROM FEEDING FRESH SUPRARENAL CORTEX, MEDULLA AND WHOLE GLAND TO THE STANDARD WHITE RAT. By EARL B. MCKINLEY and N. F. FISHER.

In controlled experiments in which standard white male rats obtained from the Wistar Institute were employed, fresh suprarenal cortex, medulla and whole gland were fed, with the following results:

Fresh whole beef suprarenal glands, kept at a temperature below freezing, proved toxic to white rats when given in 0.5 Gm. amounts. Much larger doses of fresh whole suprarenal glands removed from rabbits and cats and immediately fed to rats produced no serious effects. Epinephrin chloride when given to the white rat by mouth in amounts as great as 10 cc. of a 1:1,000 solution produced no apparent effects. When whole beef suprarenal glands were exhausted of their epinephrin content and incubated with a culture of the intestinal flora of the white rat (anaerobes excluded) and fed to rats, depression was noted. Desiccated suprarenal gland when fed in amounts varying from 5 to 10 grains (0.32 to 0.65 Gm.), invariably produced untoward results. Gastro-intestinal symptoms as described in man, following the administration of desiccated gland, are similar to those noticed in these experiments. The cortex from beef suprarenal glands may be kept as long as four days at a low temperature and be fed to rats in amounts as large as 3 Gm. per day without ill effects. Rats fed on fresh suprarenal cortex at the end of eleven weeks were 10 per cent heavier than the control animals.

The spleens of the fresh cortex fed animals were 18 per cent heavier than the spleens of the control animals, while the testes were 21.5 per cent heavier than the testes of the control animals. The increased weight of the testes in the cortex fed animals seems to justify the long thought of relation between these two organs.

STUDIES ON THE HISTOGENESIS OF AUTOPLASTIC THYMUS TRANSPLANTATION IN THE RAT. By JESSIE M. GOTTESMAN and HENRY L. JAFFE.

The lack of knowledge and the disagreement as to the origin and biologic significance of the small thymic cell have been the main stumbling blocks toward a proper understanding of the functions of the thymus gland. It occurred to us that additional information might be obtained from a detailed study of the histologic changes which occur in autoplastic thymus transplants from a few hours after their insertion to their complete regeneration.

This study is based on an examination of 212 autotransplants removed from the abdominal muscle of fifty-three young rats and fixed and stained by various methods. The transplants were examined at approximately twelve hour intervals until the one hundred sixth hour, and from then on at twenty-four hour intervals until the sixteenth day.

The work shows that autoplastic transplants undergo destructive changes which begin within a few hours and reach their height in about two days. Regenerative changes begin after forty-eight hours, and these are characterized by proliferation of the reticular cells. During the third day the small thymic cells first appear between the proliferated reticular cells, apparently as a result of enlargement and division of the latter cells. The regeneration is usually complete by the fourteenth day, when the new formed lobules are differentiated into cortical and medullary zones.

DISCUSSION

DR. WOLBACH: Replying to the question whether the thymus must be removed to produce regeneration, and whether there is a migration of small round cells into the cells, I think that the early stages look like foreign body giant cells.

DR. MARINE: I think that the Hassall corpuscles may arise from ducts of Remak. I have seen this in dogs.

DR. FOOT: In a case of tumor of the thymus which I studied, the corpuscles were found where the necrosis was most marked, and I found them in metastasis in the lung.

DR. HAYTHORN: The bodies look like foreign body giant cells, but in later stages the picture is more typical.

DR. KRUMBHAAR: I should like to know about injections of dye or India ink.

DR. BROWN: More detailed information should be given from early and late stages.

DR. JAFFE: In thymus transplants take after complete removal of the gland. I think that the thymic round cell is derived from the reticular cells. They are not lymphocytes. They are entodermal cells. The cells keratinize. There is parallelism between the Hassall structures and necrosis. When a lobe is transplanted, the Hassall corpuscles are more readily formed. I could not get the bodies outside of the thymic lobule. They are formed under the retained zone.

MOUSE EPITHELIOMA PRODUCED BY REPEATED APPLICATIONS OF PHILADELPHIA GAS TARS. By J. L. GOFORTH.

Philadelphia gas tar, "horizontal" and "vertical" types, was repeatedly applied to the same skin area of ninety-four white mice in two series, at intervals of from three to seven days, over a period of eight months. In all, seventeen tumors were produced — five in the "vertical" and twelve in the "horizontal" series. These tumors began as soft epithelial warts, usually appearing near the center of the painted area from 160 to 200 days after the first application of tar; they soon became highly keratinized, and, in the course of six weeks, seven became definitely malignant — histologically, carcinoma spinocellulare. In no instance was metastasis demonstrable. Over one half of the mice died from tar intoxication before any tumors appeared.

THE FORMATION OF INTERCELLULAR SUBSTANCES IN THE REPAIR OF EXPERIMENTAL SCORBUTUS. By S. B. WOLBACH.

In scorbutus there is a failure to maintain intercellular substances. An imperfect substance is manufactured. This is demonstrated in the teeth, where after the addition of the antiscorbutic the imperfect substance gelifies. The demonstration is readily accomplished by histologic methods.

GASTRIC SECRETION FOLLOWING VARIOUS GASTRIC OPERATIONS. By STANLEY P. REIMANN and L. SNELLBAKER.

This part of the report comprises the results of the estimation of acids before and after various gastric operations which were performed for peptic ulcers. They include simple excision, posterior gastro-enterostomy with and without excision, pylorectomy, the operations of Billroth no. 1 and no. 2, subtotal gastrectomy and the so-called Roux "Y" operation. No consistent differences from preoperative estimations were found except in the cases of subtotal resection, in which the values for the acidity were all quite low. The methods consisted of examination of the fasting stomach contents and of fractional specimens following a standard meal of 250 cc. of water and 35 Gm. of bread. The results are those of two or more examinations made at intervals of from three to six months over a period of from one to five years following these various operations. The important clinical point is that relatively more of the patients who have had subtotal gastric resection performed are in better health than the others.

A Microscopic Slide Precipitation Test for Syphilis. By B. S. Kline, A. B. Mill and A. M. Young.

The purpose of this preliminary report is to describe a microscopic slide precipitation test for syphilis with Kahn's antigen which is as sensitive as the routine three tube Kahn test, with the following advantages over that method: (1) It is simpler. (2) It requires less apparatus and much less serum. (3) The results are easier to read.

The Test.—The test is performed on microscopic slides containing on one surface four paraffin rings each about 11 mm. in diameter. Into each ring

Table 1.—*Two Hundred and Sixty-Eight Comparative Microscopic Slide Tests (Kahn Antigen) (Various Quantities Antigen Dilution and Serum) and Kahn Tests*

	Tests	Percentage
Agreement	226	84.3
Relative agreement	36	13.4
	262	97.7
Disagreement	6	2.3
Total	268	

Positive reaction = ++++, +++, and ++.
Doubtful reaction = + and ±.
Agreement = positive or negative by both methods.
Relative agreement = positive or negative by one method and doubtful with the other.

Table 2.—*Three Hundred and Fifty-Seven Microscopic Slide Tests (Kahn Antigen) Various Quantities Antigen Dilution and Serum and Wassermann Tests (Ecker Antigen, Overnight Icebox Incubation)*

	Tests	Percentage
Agreement	268	78.1
Relative agreement	51	14.9
	319	93.0
Disagreement	24	7.0
Total	343	

Wassermann anticomplementary, slide test variable; fourteen tests = 4 per cent.

0.06 cc. of the undiluted serum to be tested is delivered from a pipet. After all the serums are pipetted, 1 drop of Kahn's antigen dilution (0.015 cc.) is allowed to fall into the serum in each ring. After all the antigen is pipetted, the small amount in each ring is evenly distributed by rapidly stirring the mixture with a tooth pick (a new tooth pick with flat end a few mm. in width is used for each test). After the mixtures are complete, the slides, without further agitation, are placed in a humidor and allowed to remain at room temperature for ten minutes. At the expiration of this time, the first slide is removed, rocked and rotated by hand for about thirty seconds (about thirty times) and allowed to stand in the open air for from thirty seconds to one

TABLE 3.—*Two Hundred and Thirty-Two Comparative Slide Tests and Wassermann Tests, Kahn Antigen Cholesterolized and Non-cholesterolized, Overnight Icebox Incubation*

	Tests	Percentage
Agreement	177	80.5
Relative agreement	26	11.8
	203	92.3
Disagreement	17	7.7
Total	220	

Wassermann anticomplementary, slide test variable; twelve tests = 5.2 per cent.

TABLE 4.—*Two Hundred and Eighty-Nine Comparative Kahn Tests and Wassermann Tests (Ecker Antigen, Overnight Icebox Incubation)*

	Tests	Percentage
Agreement	232	82.3
Relative agreement	35	12.4
	267	94.7
Disagreement	15	5.3
Total	282	

Wassermann test anticomplementary, Kahn test variable; seven tests = 2.4 per cent.

TABLE 5.—*One Hundred and Ninety-Two Comparative Kahn Tests and Wassermann Tests (Kahn Antigen Cholesterolized and Non-cholesterolized, Overnight Icebox Incubation)*

	Tests	Percentage
Agreement	165	88.2
Relative agreement	12	6.4
	177	94.6
Disagreement	10	5.4
Total	187	

Wassermann test anticomplementary, Kahn test variable; five tests = 2.6 per cent.

minute before examining. Before reading the first slide, the second slide and the third one if used are rocked and rotated, allowed to remain in the air for from thirty seconds to one minute and then read. The readings are made through the microscope (16 mm. objective, 10 or 12.5 eyepiece) with the light cut down as in studying urinary sediments and recorded in terms of pluses according to the size of the clumps.

As will be seen from the tables, there is a close agreement between the microscopic slide precipitation test, the Kahn test and the Wassermann test.

PARTIAL DESTRUCTION OF THE SINO-AURICULAR NODE IN DOGS' HEARTS WITH ELECTROCARDIOGRAPHIC AND HISTOLOGIC STUDIES. By MILTON C. BORMAN and THOMAS H. MACMILLAN.

A preliminary report is given of the effect on cardiac mechanism as detected by the electrocardiogram, of destruction of the sino-auricular node in dogs' hearts with radium.

In the first series of fourteen dogs, the method employed was surgical excision and ligation, which gave unsatisfactory results. In the second series of eighteen dogs, the destruction was accomplished by radium emanation. This method has yielded excellent results. The findings obtained reveal that in each of five animals part of the body and tail of the node were included in the area of acute inflammation, with degeneration, necrosis and ultimate scar tissue formation. In four other animals, the tails of the nodes were considered to be affected. While no attempt was made to destroy the node entirely, a temporary suppression of functional activity was brought about in two animals. Of the remaining nine animals, five have revealed no changes, due to faulty technic, and four still remain to be studied.

The average of the latter method as compared with others utilized in the past for similar purposes was discussed. Lantern slides were used to illustrate the histologic and electrocardiographic changes produced by radiation of the node.

CHRONIC LIGNEOUS THYROIDITIS (RIEDEL'S STRUMA): FIVE CASE REPORTS WITH PATHOLOGIC NOTES. By LAWRENCE WELD SMITH.

Chronic ligneous thyroiditis is still such an obscure disease, with less than thirty accepted cases in the literature, that the recording of any additional cases is justified in an attempt to solve the problem. Accordingly, five cases occurring in nearly 1,200 thyroid admissions at the Lahey Clinic of the New England Deaconess Hospital during the past two years are presented. These were all in women between 49 and 67 years of age, and represent apparently the progressive changes to be seen in the course of the disease. Histologic studies rule out tumor and both tuberculosis and syphilis as etiologic factors, and force the conclusion that the condition is the result of some low grade inflammatory process, although experimental attempts to reproduce the lesion have been uniformly unsuccessful.

TRANSPLANTATION AND POTENTIAL IMMORTALITY OF MAMMALIAN TISSUES. By LEO LOEB.

In 1901 and the following years Dr. Loeb, on the basis of long continued transplantations of mammalian tumors extending through many consecutive generations and in which he could show that after transplantation the peripheral cells of the transplant remained alive and gave origin to the new tumor, came to the conclusion that tumor cells are potentially immortal, and that this applied

to various kinds of tumor tissues, those of epithelial as well as of connective tissue origin. As it was evident that tumor cells merely represent ordinary tissue cells which under the influence of certain growth stimuli and specific conditions favoring proliferation became transformed into tumor cells, he drew the further conclusion that also the mammalian tissues from which such tumors take their origin are potentially immortal.

Subsequent experiments on transplantation of normal mammalian tissues showed that serial transplantation comparable to the method used in the case of tumors was apparently not applicable in the case of normal tissues, because under "homoio" conditions lymphocytes and connective tissue of the host actively invade the transplant and destroy it in the course of time. However, more recent experiments in which cartilage was used have shown that while in principle cartilage behaves after homoiotransplantation like other mammalian tissues, as typical lymphocytic and connective reactions occur, there exist some quantitative secondary differences which make it possible to carry out serial transplantations with cartilage comparable to those carried out with tumors. Thus, it has been possible not only to transplant serially the cartilage of young animals — rats were selected for these experiments — but also the cartilage of very old animals which were approaching an age when they tend to die spontaneously.

The xiphoid cartilage of rats 2 or 3 years old were transplanted serially, and in several cases the cartilage was kept alive and proliferating for two or three years and even for more than three years, so that the living cartilage at the time of examination had reached an age somewhere between 5 and 6 years. In several cases cartilage about 5 or 6 years old was to a great extent preserved; in other cases parts of it were alive and still proliferating. These results suggest strongly the conclusion that if conditions are favorable, it may be possible to transplant adult cartilage serially for a long period of time and perhaps indefinitely.

Observations on the Parathyroid Glands of Rabbits Irradiated with Ultraviolet Light. By J. H. B. Grant and Frederick L. Gates.

The demonstration of an hypertrophy of the parathyroid tissue of rabbits exposed to the quartz mercury arc lamp led to a comparison of the behavior of irradiated, or partially parathyroidectomized, rabbits with normal animals, under certain experimental conditions.

Rabbits subjected to partial parathyroidectomy after irradiation with the quartz mercury arc lamp differed from normal rabbits, subjected to an identical operation, in the absence of tetanic symptoms, in a more rapid recovery from the initial drop in blood calcium, which was itself less than in the controls, and in the virtual absence of a rise in blood phosphorus, secondary to the fall of blood calcium after the partial parathyroidectomy. These experiments indicate that the parathyroid hypertrophy induced by the radiations is a true hyperplasia of functionally active tissue.

No significant differences were noted between normal, irradiated and partially parathyroidectomized rabbits in the rapid return of their blood calcium to its former level after intravenous injections of calcium chloride. While parathyroid function is essential to the maintenance of a normal level, the upper limit of blood calcium concentration is regulated by factors independent of parathyroid control.

A subcutaneous injection of disodium acid phosphate was followed by a sharp rise in blood phosphorus and a corresponding drop in blood calcium. In the rabbits which survived, this primary rise was checked by a rapid

elimination of the excess phosphate and the early return of the blood phosphorus approximately to its former level. In other rabbits, due to phosphorus retention, the blood phosphorus subsequently rose to even higher levels, and although this further rise was not accompanied by a further drop in blood calcium, these animals died of tetany. No clearly marked differences separated the normal, irradiated or partially parathyroidectomized groups in this experiment, the significance of which lies in the late difference in the blood phosphorus levels and in the Ca/P ratio, between the survivors and those that succumbed.

An experiment to determine the effect of an excess or a lack of parathyroid tissue on the retention of calcium and phosphorus during inanition did not show striking differences between normal, irradiated or partially parathyroidectomized rabbits in this respect. It was observed, however, that the irradiated rabbits lost weight more rapidly, and that several of them died without obvious lesions during the short fasting period, indicating a more active metabolism under the stimulus of ultraviolet light.

THE EXPERIMENTAL PRODUCTION OF SYMMETRICAL LEAD GANGRENE. By CARL VERNON WELLER.

The oral administration of small amounts of white lead to guinea-pigs results in a secondary anemia and progressive loss of weight. If death occurs, it may or may not be preceded by convulsions. In much larger amounts, evidences of meningo-encephalopathy appear within a few days, and death follows one or more epileptiform convulsions. However, if these larger doses are given in properly spaced series, a fatal outcome may be avoided, and such guinea-pigs can endure an intake of lead of an amount ordinarily impossible. By this method there can be produced in certain animals a symmetrical gangrene of the pinnae. The margins become necrotic, with a proximal hyperemic zone, dry down and finally are cast off, leaving irregularly notched and somewhat thickened margins. The character and course of these lesions are those of a symmetrical ischemic dry gangrene.

A MODIFIED SERUM TUBE FOR TISSUE CULTURE. By FRANK A. MCJUNKIN.

The modification consists of a spherical bulb at the end of the ordinary tube used for serologic purposes with two flattened surfaces so that the tissue growth can be examined with the oil immersion. To examine the culture the tube is clamped horizontally to a buret stand and placed below the objective with one surface exactly parallel to the Abbe condenser removed. Directions are given for making the tube, which can be done inexpensively by one with little experience in glass blowing.

THE RESPIRATION OF THE GLANDERS BACILLUS. By M. H. SOULE.

The present investigation was carried out using methods and apparatus that had been developed during previous studies on microbic respiration. By the use of the compensation manometer the pressure changes taking place in the respiratory chamber were observed, and samples of the gaseous atmosphere were removed for analysis. The culture mediums were also analyzed for carbon dioxide. It was possible to determine the total amount of oxygen consumed, the total quantity of carbon dioxide (dissolved, combined and gaseous) produced, and thus calculate the respiratory quotient.

The average respiratory quotient, when grown on glycerol agar, was 0.859; on plain agar, 0.841; on glucose agar, 0.969; on blood agar, 0.848; on autoclaved potato, 1.044; on asparagin agar, 1.21; on glucose asparagin agar, 1.12; on

sodium malate agar, 0.894. These results closely approximate theory, and indicate that the amino acid was completely oxidized to carbon dioxide and water by the germ for growth energy.

In the absence of free oxygen no growth took place, but atmospheres containing as low as 0.1 per cent of this gas, when 30 cc. were available at this low tension, gave excellent cultures. Tensions of oxygen as high as 100 per cent had no inhibitory action. Carbon dioxide in excess of 60 per cent showed some inhibition, but satisfactory cultures were obtained in the presence of 90 per cent carbon dioxide and 10 per cent oxygen. The presence of carbon dioxide was not found to be essential for the growth of the organism.

THE HEMOGLOBIN OF STRIATED MUSCLE. By G. H. WHIPPLE.

The muscles of the leg and back show a great range in their muscle hemoglobin content, which appears to depend on exercise and to determine largely the latent muscular power. Puppies 2 or 3 months of age may average 100 mg. of muscle hemoglobin per hundred grams. At 4 months there may be a rise to 200 mg., and at 6 or 7 months to 200 or 300 mg. At puberty (8 or 9 months) we are likely to see a sharp jump in the curve to 400 or 500 mg. per one hundred grams muscle tissue. Adult dogs may vary all the way from 400 mg. in a quiet house dog to 1,000 mg. in an active, trained hunting dog.

The diaphragm shows high values during the first and second month of life above the muscles of the leg. Not until near puberty does the diaphragm fall a little behind the muscles of the leg in hemoglobin content.

The flat muscles of the trunk (recti and pectorals) are uniformly below the muscles of the leg in hemoglobin content.

The heart is much more uniform in its muscle hemoglobin content, just as is its work more steady and uniform than the work of the skeletal muscles. In the first few months of life the hemoglobin content of the heart muscle may be 100 to 200 mg. per one hundred grams. It may rise slowly to 300 at puberty, and may never go much above this in a quiet house dog. Heart muscle values may range from 300 to 450 for common adult dogs. Unusual exercise may push these values up to 700 mg. of muscle hemoglobin per one hundred grams. We may see the same values with cardiac hypertrophy due to chronic nephritis and emphysema.

A quantitative method for the estimation of muscle hemoglobin is described.

Normal dogs may have from 25 to 40 per cent of their entire body weight represented as striated muscle tissue.

Representing total circulating hemoglobin of the dog as 100 Gm., we may find the total muscle hemoglobin amounting to from 10 to 80 Gm. in widely different conditions. It is obvious that muscle hemoglobin is of importance whether one studies the end products of hemoglobin disintegration or the parent substances suitable for construction into mature hemoglobin. Muscle hemoglobin must be considered in any study of body pigment metabolism.

Prolonged severe anemia may reduce slowly the level of muscle hemoglobin. When the original level was high, the reduction may even amount to 30 or 40 per cent. If the dogs are healthy and active, this reduction will scarcely go below 400 or 500 mg. muscle hemoglobin per one hundred grams. There may be even lower normal values in house dogs. We believe that exercise is more important than anemia in determining the muscle hemoglobin level in the dog.

Anemia demands cannot rob the striated muscle of its hemoglobin. The body ranks the necessity for muscle hemoglobin on a par with the need for blood hemoglobin, and from the standpoint of survival of the individual this

is a fortunate circumstance. It also shows the importance of muscle hemoglobin in body economy and general pigment metabolism.

Muscular paralysis (sciatic nerve section) is followed by a fairly rapid loss of muscle hemoglobin, becoming more noticeable from week to week. After a period of seven weeks, some muscles may contain only one-half the muscle hemoglobin found on the control normal side.

OBSERVATIONS ON THE SPECIFIC TOXEMIA OF SCARLET FEVER. By F. G. BLAKE and J. D. TRASK.

A study was made to determine the amount of toxin found in the blood of 144 cases of scarlet fever. The blood was injected intracutaneously into susceptible individuals. In severe cases as many as 350 skin test doses were found and as few as 40; in moderate cases from 25 to one-quarter skin test doses. In a normal run of cases the specific toxemia falls at the end of the first week; in septic cases in the second and third week.

DISCUSSION

DR. ECKER: Were the specimens of blood typed prior to injection and tested particularly for isohemolysins?

DR. PAPPENHEIMER: Were cases of nephritis studied?

DR. TRASK: The specimens of blood were not typed, but reactions due to isohemolysins appeared early and disappeared at the end of about six hours, while the toxic reactions appeared in twenty-four hours. No cases of nephritis were studied.

EFFECT OF HYDROGEN ION CONCENTRATION ON SWELLING OF CELLS. By BALDUIN LUCKÈ and MORTON MCCUTCHEON.

Study of the changes in size in living cells resulting from changes in the composition of the fluid medium in which they exist is fundamentally important both for physiology and pathology. Many investigations of the swelling of nonliving material, such as gelatin, have been made and inferences have been drawn, thought to be applicable to living tissue cells. Erythrocytes, because of their convenient availability, have frequently served as objects of this type of study. But it seems definitely certain that results obtained from dead proteins cannot be transferred to living protoplasm; and erythrocytes, from the standpoint of structure, vitality and chemical composition, can hardly be regarded as similar to the majority of animal cells.

We have sought to study the effects of acids and alkalis on the volume of cells which, in structure and composition, more closely resemble tissue cells and which in addition can be made to exhibit a definite criterion of life: for only in a cell possessing the latter attribute can one discover whether or not the production of an effect is dependent on damage to vitality. The cells chosen were unfertilized eggs of Arbacia; they are spherical, and hence easily measurable; they behave as if surrounded by a definite membrane, and their vitality can be approximately estimated by determining their response to fertilization. In one series of experiments, various lots of eggs were subjected to changes in the reaction of the surrounding medium, a p_H range of from 3 to 9.8 being established by the addition of HCl or NaOH to neutralized sea water. Living eggs did not undergo change in size; only after they were severely damaged, as shown by subsequent fertilization experiments, did swelling occur. Similar results were obtained when carbon dioxide and ammonium hydroxide were used. Work by others has shown that erythrocytes swell immediately under condi-

tions similar to those which we have tested; this result is interpreted to mean the passage of ions into the cell, with consequent increase in osmotic pressure and attraction of water, in accordance with the permeability of the membrane and the laws of membrane equilibrium as formulated by Donnan. Our experiments show an entirely different response to acids and alkalis on the part of Arbacia eggs, and indicate that as long as the cell is uninjured a "Donnan equilibrium" such as occurs in erythrocytes is not established in the cells investigated by us.

THE KINETICS OF OSMOTIC SWELLING IN ARBACIA EGGS. By MORTON MCCUTCHEON and BALDUIN LUCKÉ.

The volume of living cells is conditioned by a number of factors, an important one being the concentration of the surrounding medium with which the cell contents are in osmotic equilibrium. In order to study the rate of volume change resulting from osmotic changes and the conditions that influence this rate, it is necessary to use isolated cells, the viability of which can readily be tested. An almost ideal cell for such an investigation is the unfertilized egg of the sea urchin. In the present study it is shown that the rate of swelling of these cells follows well-known diffusion laws, but that because of the presence of a semipermeable membrane enveloping the cells, other factors than diffusion come into play. The regularity with which the various processes pursue their course is such that events may be calculated; and it is found that a good agreement exists between the observed and the calculated results.

The rate of swelling of Arbacia eggs in hypotonic sea water, over wide ranges of temperature and concentration, is found to follow the equation $kt = \text{In} \frac{V_{eq} - V_o}{V_{eq} - V_t}$, when V_{eq}, V_o, and V_t are volumes at equilibrium, at first instant, and at time t, respectively, and k is the velocity constant (Lillie, R. S.: Am. J. Physiol. **40**:249, 1916).

The rate of swelling, while primarily regulated by diffusion forces, is influenced also by other processes occurring in the semipermeable membrane. Evidence for this assertion is furnished by the effects of temperature and of concentration on the rate.

Calculations made from the values of k at various temperatures show that the temperature coefficient is high, from 2 to 3 for a change in temperature of 10 degrees corresponding to a chemical rather than to a diffusion process. Calculated from the Arrhenius equation, the heat of activation ranges from 13,000 to 19,000 calories.

The rate of swelling is greatly affected by the osmotic pressure of the sea water. It requires very much longer for the cells to reach equilibrium in a mixture of 40 parts of sea water to 60 of distilled water than when 80 parts of sea water to 20 of distilled water are used. There is a corresponding change in the velocity constants. In a typical experiment at 15 C., the value of k in 20 per cent sea water was 0.006; in 40 per cent sea water 0.012; in 60 per cent sea water, 0.024; and in 80 per cent sea water, 0.072.

On these grounds, it is concluded that processes of unknown nature occur in the semipermeable membrane, and modify the effect of diffusion.

KETOSIS IN THE RAT. By ARTHUR H. SMITH and HAROLD LEVINE.

It was found that the output of acetone bodies in rats could not be increased by dietary means. This was later accomplished by the addition of sodium bicarbonate to the diet. In a qualitative way, the rat does not vary in this respect from man. The difference is quantitative.

Book Reviews

PHYSICAL CHEMISTRY IN BIOLOGY AND MEDICINE. By J. F. MCCLENDON, PH.D., Professor of Physiologic Chemistry at the University of Minnesota Medical School, and GRACE MEDES, PH.D., Assistant Professor of Physiologic Chemistry at the University of Minnesota Medical School. Cloth. Price, $4.50. Pp. 425, with illustrations. Philadelphia: W. B. Saunders Company, 1925.

The contents of this book are suggested by the chapter headings: 1. Mass and Volume, 2. The Colloid Particle, 3. Intermolecular Forces, 4. Electrolytic Dissociation and Chemical Equilibria, 5. Hydrogen Ions, 6. Radiant Energy, 7. Atomic Structure and Physiologic Action, 8. Thermochemistry in the Living Body, 9. Colloids in Organisms, 10. Hydrogen Ions in Biology, 11. Ionic Equilibria in Blood, 12. Osmose, 13. Permeability, 14. Surface Forces.

In the presentation of original work elegance of exposition is of secondary importance. If the facts are set forth, if the idea is made evident, the author may rise to greatness in spite of bad grammar. Furthermore, limitation of journal space has imposed the condensed style in which citation and the expression "it can be shown" have been substituted for true exposition. Under these new literary standards the expositor must exert himself to the utmost of his capability to escape the illusion that he is explaining when he merely assembles facts and ideas which recall to his own mind the logical development of a concept.

The authors of "Physical Chemistry in Biology and Medicine" are contributors to the literature of original research; but their book must be judged by standards which apply to expositors.

In developing the equation for the maximum work of gases, an attempt is made to break the curse of the modern invocation "it can be shown." But the detail presented is largely mathematical and at the expense of those niceties of thermodynamics which should have been carefully explained before being lost in the various applications of the equation. Then the curse descends, and throughout the remainder of the book important equations are introduced with the remark that A "has shown the following equation to be applicable."

Of mechanistic in contrast to mathematical exposition it may be remarked that it is a pity that so little use was made of the theory of atomic structure. Pretty pictures of the orbits in the Bohr atom are shown, but the coordinating and simplifying consequences of the most elementary aspects of the subject are hardly mentioned.

In some chapters dishes of theory are so heavily peppered with details of experimental technic that it is difficult to distinguish bone from tenderloin. Other chapters require no sharpened wits, for they are courses of tidbits culled from what must be a huge cache of card indexes.

The reference lists will be valuable to many workers, yet even here are defects. Perhaps the size of Cowdry's "General Cytology" and Neuberg's "Der Harn" caused them to be cited at the end of the chapter on mass and volume. Certainly none of the other references in this section are appropriate to the chapter. The title of Sörensen's classic paper on indicators and standard buffers

caused it to be listed under enzymes, and the other references on indicators and buffers are not well selected.

Neither the data on standard buffer solutions nor data essential to a workable knowledge of other subjects are conveniently tabulated.

To isolate a sentence from its context is often unfair, yet the authors themselves have the habit of throwing in sentences which are so isolated from the surrounding text that they fail to convey meaning. Fair examples are:

"Indicators are weak acids or bases. The mathematical relations of the latter are the reciprocal of those of the former."

"Since light may cause oxidation of an atom it seems unnecessary to look for a further explanation of the destructive action. It has been shown that proteins may be coagulated by ultraviolet light."

"Light from 295 to 380$\mu\mu$ is absorbed by the lens and transformed into visible light."

"Since the bodies of animals consist of over 60 per cent. water, most of the substances in them are in solution."

Those who are familiar with the subjects treated will find the text and reference lists useful to stir the recollection; but this is not the avowed purpose of the book. McClendon and Medes, contributors to the literature of original research, admirably visualizing the needs of biochemists and responding to a call in a better than missionary spirit have simply failed to master the art of exposition. It is a pity that this fault has ruined an admirably conceived treatise.

THE CHEMICAL ACTION OF ULTRAVIOLET RAYS. By CARLETON ELLIS and ALFRED WELLS, with the assistance of Norris Boehmer. Price, $5 net. New York: The Chemical Catalog Company, Inc., 1925.

Medical interest in photochemical effects is by no means recent. The work of von Tappeiner and his school, the early work of the bacteriologists on the effects of light on bacterial life and the studies of Finsen that developed from this lead, readily come to mind. In recent years the field has broadened with the inclusion of systemic light effects.

The medical investigator is handicapped in this study because of the diffuse scattering of pertinent literature. Even the established facts underlying the physical and chemical basis of light effects are not readily accessible. A monograph embodying a complete review of the subject of ultraviolet rays might seem a welcome addition to the biochemical library. Such a review has been prepared by Ellis and Wells. It covers the subject without being verbose; it is clear, the material reviewed is properly digested and correlated, the references seemingly correct. There is a complete description of apparatus and of protecting devices. Several chapters are devoted to the theory of the photochemical mechanism and a discussion of ultraviolet effects in organic as well as inorganic chemical processes. These chapters are particularly satisfactory, as are also those on halogenation and photosynthesis. The concluding divisions include sterilization, biologic effects and therapeutic and technical applications.

It is not to be expected that the biologic discussion will include all the literature that has accumulated. Pfeiffer's work, or the effects of light on certain skin lesions—including pellagra—are, for instance, omitted. For the medical reader this is of no consequence, for the value of the book lies in its presentation of the more strictly chemical side of the problem. This field it covers and summarizes in a most useful way.

LEHRBUCH DER PHYSIOLOGISCHEN UND PATHOLOGISCHEN CHEMIE. PROF. DR. OTTO FÜRTH, Lepzig: F. C. W. Vogel, 1925.

In 1911 Fürth published his lectures on "Problems of Physiological and Pathological Chemistry," which were later translated into English by Allen J. Smith and published in this country under the title "The Chemistry of Metabolism." The new edition appears in a greatly altered form. In the "Problems" Fürth assumed a knowledge of the elements of biochemistry on the part of his audience, but in the "Lehrbuch" he has incorporated a brief but systematic discussion of the entire field of physiologic chemistry as related to the problems under consideration. This treatment has expanded the work into two volumes, in some respects a disadvantage; but perhaps the field of usefulness has been widened. The first sixteen of the entire series of seventy-five lectures appears in this first installment, covering the chemistry of the tissues and the blood, including discussion of the chemistry of the proteins, carbohydrates and lipins, as well as of the blood constituents. Like all of Fürth's productions, this work is characterized by an excellent balance of the subject matter and a delightfully clear and readable presentation. The author's unusually wide acquaintance with many sides of both biologic and medical problems, his clear vision of the relation of the individual items of knowledge to the entire scheme of biology, and his exceptional familiarity with the world literature, give these lectures a quality of breadth and inspiration scarcely to be found elsewhere in this field. The problems of the physician and the pathologist receive the same consideration as those of the biologist and the chemist, from the broadest of points of view. Fürth's "Lehrbuch" should not only be on the desk of every pathologist, physiologist and biochemist, but it is to be hoped that it will become familiar to the student of medicine, not merely for the wealth of material it contains, but especially for the clear vision and judicial attitude, so well displayed that they cannot fail to be of sound influence on the developing intellect. As an example of the author's style and attitude, the following paragraph is quoted, which will certainly meet the approval of pathologists: "According to recent investigations it is possible to distinguish under the microscope, by staining methods, four sorts of fatty substances in the tissues: neutral fats, lipoids (already present during life), myelins (appearing only after death), and cholesterol esters. It is clear that only through thorough chemical investigations, carried along hand in hand with the morphologic demonstrations, can be determined the value of such differentiation. But it is a source of satisfaction that gradually the morphologists are becoming permeated with the recognition that differentiation by staining methods is nothing else than a special form of chemical or physicochemical reaction, and that it is most earnestly to be desired that these should be complemented by better defined chemical methods. The enormous increase in the scope of knowledge continually gives rise to new specialization and new boundaries. Because of the unfortunately limited capacity for comprehension by the human brain, this cannot be avoided. Nevertheless, the chemist, who only squats between his reagent glasses and boxes, ignoring with intent and conviction all things that he cannot boil, extract and distill, fits as little into the picture of modern science as the morphologist who considers nothing worth considering except his stained sections. A free viewpoint alone will satisfy those who, finding the thickets of the lowlands too crowded, struggle towards the heights."

ENTWICKLUNG UND BIBLIOGRAPHIE DER PATHOLOGISH-ANATOMISCHEN ABBILDUNG. By EDGAR GOLDSCHMID. Price, 150 marks. Pp. 301, with 44 illustrations. Leipzig: Karl W. Hiersemann, 1925.

This is the first serious attempt to grapple with a theme of some moment to medicine, namely, the history of pathology. Pathology, as a generic term, connotes and comprises everything relating to the essential nature of disease. In ordinary usage, however, it denotes the changes in structure and function produced by disease and thus includes both the "anatomical idea" of Virchow and what Allbutt styled "altered physiology," i. e., the facial appearance and physical habitus in different diseases, as well as in paralytic deformities and other derangements of function. The plates in the present volume cover changes in the external configuration of the face and body (semeiology) as well as pathologic changes in structures beneath the skin. It is plain that this phase of the history of pathology is largely the history of its delineation by skilled artists. The author, a Frankfurt professor and prosecutor in the Senckenburg Pathological Institute, has therefore followed the ground-plan of Choulant's famous "History of Anatomical Illustration" (1852). If his adherence to the Choulant tradition seems a bit too formal at times, it is to be remembered that his model is one of the greater classics of medicine, a work of infallible accuracy, representing a lifetime of patient research. His book begins with a sketch of the history of pathological illustration, including the technical processes of reproduction. This is followed by a brief bibliography of source-books, after which the author launches bravely into a complete reasoned bibliography of books containing pathologic pictures, arranged in five chronologic periods. There follow valuable and accurate indexes of authors, artists, publishers and books (under authors' names), a subject-index of the diseases and parts of the body illustrated in the different atlases and an index of the forty-four plates, twenty-eight of which are handsomely colored.

The prehistory of the subject comprises accidental figuration of pathologic formations on antique vases, stelae, papyri, frescoes, old manuscripts, primitive pottery, ex voto tablets and the like. Between this phase and the period of conscious or intentional illustration of pathology come the chance figurations on fugitive sheets, in nonmedical books, oil paintings, sculpture of the post-antique period and so on. Examples of the early phases, as presented in the plates, are a votive tablet from Athens representing varicose veins, a bit of Huaco sculpture showing facial paralysis, terra-cotta figurations of the facies of disease from Asia Minor, Albert Dürer's colored print of syphilis, Ghirlandajo's rhinophyma and a painting of Simon Vouët's showing suppurative osteomyelitis. The first period of illustration with didactic intention begins with the start made in first-class anatomic illustration by Leonardo da Vinci and Vesalius and goes down to the time of the great surgeon anatomists of the 18th century (1517-1733). It is the period of wood and copper plate engraving and etching, illustrated in the volume by cuts from Bonetus (1686), Valentini (1715) and Heister (1715). The second period, from Cheselden to Soemmering (1733-1792), is the period of the surgeon anatomists who produced great atlases in copper and steel engraving. The third period, from Sandifort to Cruveilhier (1793-1829), marks the rapid victory of colored lithography over colored copper plates, splendidly exemplified in the pathologic reports of Richard Bright (1827-1831). The fourth period (1830-1860) finds its high spots in the atlases of Cruveilhier (1829-1842), Carswell (1838), Lebert (pathologic histology, 1845), Danielssen and Boeck on leprosy (1848), Auvert (1851), in the work of the dermatologists and in *Virchow's Archiv* (1847-1925). The fifth period runs from 1860 to the

recent developments of chromolithography, photography and the low-priced hand-atlases. The colored plates illustrating these periods are of superlative excellence, particularly those from Cruveilhier, Lebert, Auvert and the dermatologic atlases of Alibert (1817-1828), Bateman (1830) and Rayer (1839). One misses, it is true, the Venus of Willendorf, the earliest known bit of prehistoric sculpture (showing the endocrine phase of obesity), the achondroplastic dwarf figurines of Egypt, collected by Charcot, the pathologic plates of Richard Bright (1827), Corrigan's superb engraving of aortic insufficiency (1832), the facies of Addison's disease (1855) and the wonderful iconography of nervous diseases made under the inspiration and guidance of Charcot. The *Nouvelle Iconographie de la Salpêtrière* is, in fact, treated with scant courtesy. Our author does not seem to realize that it consists of twenty-eight stout volumes (1888-1918) containing the most valuable illustrations of the pathology and semeiology of nervous diseases in existence. These pictures show not only the facies and habitus in typical cases, but, in accordance with Charcot's teaching, carefully selected atypical or incipient cases, so that a person with a tendency to acromegaly or exophthalmic goiter might be recognized, say, in a street-car. The excellent *Revue photographique des hôpitaux de Paris* (1869-1872) is also omitted. These, however, are slips which it will be easy to correct in a subsequent edition. The book is obviously a vade mecum for all medical librarians and will find its way into the collections of professional pathologists who care for their subject. The format is, if anything, too massive and sumptuous. A later edition in smaller size, and with a more definite choice of pictures, would be a valuable acquisition for the active practitioner and surgeon.

F. H. Garrison

Army Medical Library, Washington, D. C.

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